PREVALENCE OF SHUNT DEPENDENCE AND CLINICAL OUTCOME IN PATIENTS WITH MASSIVE INTRAVENTRICULAR HAEMORRHAGE TREATED VIA ENDOSCOPIC WASHOUT VERSUS EXTERNAL VENTRICULAR DRAINAGE

By

DR. JASON RAJ A/L JOHNSON

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CT	Computed Tomography
MRI	Magnetic Resonance Imaging
IVH	Intraventricular haemorrhage
ICB	Intracerebral heamorrhage
AVM	Arteriovenous malformation
BG	Basal Ganglia
CSF	Cerebrospinal Fluid
CVA	Cerebrovascular accident
ED	Emergency Department
ICU	Intensive Care Unit
HDU	High Dependency Unit
HUSM	Hospital University Science of Malaysia
HKL	Hospital Kuala Lumpur
EVD	External Ventricular Drainage
GCS	Glasgow Coma Score
GOS	Glasgow Outcome Score
mRs	Modified Rankin Scale Score
DM	Diabetes Mellitus
HTN	Hypertension
IHD	Ischemic Heart Disease
MAP	Mean Arterial Pressure
ADL	Activities of Daily Living

ABSTRAK

Tajuk: Kajian Kebarangkalian Pesakit Dengan Pendarahan Dalam Sistem "Ventricle" Yang Dirawat Dengan "External Ventricular Drainage" Berbanding Dengan "Endoskopic Washout" Yang Memerlukan Shunt Untuk Aliran Cecair Otak : Kajian Intervensi dengan Control Historical

Pengenalan: Pendarahan dalam system "ventricle" otak adalah entiti klinikal yang sering ditemui di hospital yang mempunyai perkhidmatan neurosurgeri. Keadaan ini biasanya disebabkan oleh pendarahan dalam otak primari yang akan melibatkan sistem "ventricle" dimana aliran cecair otak akan tergangu. Apabila keadaan ini berlaku dan aliran cecair otak tidak lancar, sistem "ventricle" akan kembang dan memyebabkan keadaan yang dikenali sebagai hydrocephalus. Seterusnya, ini menyebabkan peningkatan tekanan dalam otak dan memyebabkan pesakit berada dalam keadaan coma atau kurang sedar untuk jangka masa yang panjang. Selain itu, produk sampingan yang dihasilkan daripada pecahkan sel darah akan turut mengalir dalam cecair otak dan merosakkan "arachnoid granulations" dan menyebabkan hydrocephalus berkomunikasi lewat. Ahkirnya, semua ganguan ini akan menyumbang kepada morbiditi dan mortaliti pesakit yang terlibat. Pengurusan standard semasa IVH adalah dengan memasukkan saliran ventrikel luaran (EVD) kateter. Walau bagaimanapun, prosedur ini hanya menangani masalah hydrocephalus akut dan peningkatan tekanan otak.

Objektif: Tujuan kajian ini dijalankan adalah untuk membandingkan peratusan pesakit yang mengalami pendarahan dalam sistem ventricle yang dirawat dengan cara “endoscopic washout” banding dengan cara “external ventricular drainage” yang akhirnya memerlukan “shunt” untuk membantu dalam aliran cecair otak. Selain itu, kajian ini juga melihat perubahan dalam “Graeb skor” antara dua jenis rawatan ini. Graeb score adalah satu sistem untuk mengklasifikasikan pendarahan dalam ventricle dengan objective. Skor ini diterangkan dengan sepenuhnya di dalam proposal dissertasi yang disertakan. Tahap peningkatan dalam neurologi pesakit juga dikaji dalam masa 3 & 6 bulan. Neurologi pesakit akan diberi skor berdasarkan sistem “Modified Rankin Scale” dan peratusan pesakit yang mengalami jangkitan kuman selepas menerima rawatan yang dinayatakan akan dibandingkan antara 2 jenis rawatan yang diberi. Akhirnya, kajian ini mencari kaitan antara faktor pesakit seperti (umur, jantina, skor GCS asal masa pesakit diterima) dengan tahap neurology dalam masa 3 dan 6 bulan.

Kaedah: Kami telah merawat 16 pesakit dengan pendarahan sistem “ventricle” otak dengan kaedah endoskopik washout sepertimana dinyatakan dalam protokol kajian untuk menangani semua sekuelanya yang tidak diingini disebabkan oleh keadaan neurosurgikal ini. 23 pesakit penyakit yang sama telah dirawat melalui saliran ventrikel luar (EVD).

Keputusan: Semua pesakit yang dirawat dengan kaedah endoskopik washout pulih dengan baik dan hanya 3 pesakit memerlukan pembedahan lanjutan untuk meletak shunt dalam jangka masa 3 bulan. Terdapat perbezaan yang signifikan dalam kebergantungan kepada shunt untuk mengalirkan cecair otak di antara kedua-dua kawalan dan kumpulan intervensi (p-0.004). Tempoh kebergantungan kepada kateter ventrikular luar (EVD) adalah jauh lebih pendek dalam kumpulan endoskopik wahout berbanding dengan kumpulan kateter ventrikular luar (p-0.007) Selain itu, pengurangan skor Graeb adalah lebih ketara dalam kumpulan endoskopik washout (p-0.001).

Kesimpulan: Hasil yang baik diperoleh daripada kaedah endoskopik washout untuk pendarahan intraventricular yang serius mungkin berkaitan dengan penyingkiran awal hematoma, penciptaan baru lencongan laluan cecair otak, ditambah dengan jangka masa pendek yang diperlukan untuk kebergantungakan kepada kateter ventrikular luar (EVD) dan ventilator. Oleh itu, penggunaan neuroendoscopy pada pesakit dengan pendarahan intraventricular yang serius berjaya mengurangkan pergantungan kepada shunt dan dengan itu semua komplikasi yang berkaitan dengan shunt juga dielakkan.

Kata kunci: Pendarahan intraventricular serius, skor Graeb, kaedah endoskopik washout, arachnoid granulations

ABSTRACT

Title: Prevalence of shunt dependence and clinical outcome in patients with massive intraventricular haemorrhage treated via endoscopic washout versus external ventricular drainage**.**

Background: Intraventricular haemorrhage (IVH) is a commonly encountered neurosurgical emergency in most clinical centres. It is most prevalent in cases of hypertensive intracerebral haemorrhage (ICH) with extension into the ventricular system. This neurosurgical entity contributes to morbidity & mortality via blockage of ventricular conduits causing hydrocephalus and increased intracranial pressure, prolonged reduced level of consciousness and damage to the arachnoid granulations leading to delayed communicating hydrocephalus. Current standard management of IVH is by insertion of external ventricular drainage (EVD) catheter. However, this procedure only addresses the problem of acute hydrocephalus and raised ICP.

Objective: The aim of this study is to evaluate the benefits of endoscopic washout surgery for treatment of massive intraventricular haemorrhage in terms of prevalence of drainage dependency, risks of external ventricular drain infection and to assess the functional outcome of the patient as compared to those treated via external ventricular drainage alone.

Methods: We have treated 16 patients with massive IVH with endoscopic washout as per study protocol to address all the undesired sequelae caused by IVH. 23 patients of the same disease were treated via external ventricular drainage.

Results: All patients treated with endoscopic washout recovered well and only 3 patients required further shunt surgery at 3 months duration. There is significant difference in the shunt dependency between both control and intervention group (p-0.004). The duration of weaning of the external ventricular catheter is significantly shorter in the endoscopic washout group (p-0.007) and the Graeb score reduction is significantly more in the endoscopic washout group (p-0.001).

Conclusions: Good outcomes obtained from endoscopic washout for massive intraventricular haemorrhage may be related to early removal of hematomas, creation of new cerebrospinal diversion pathway, coupled with early weaning from external ventricular drain and ventilator. The use of neuroendoscopy in patients with massive IVH has significantly reduced the drainage dependency and therefore all shunt related complications are also avoided.

Keywords: Massive intraventricular haemorrhage, Graeb score, endoscopic washout, arachnoid granulations

INTRODUCTION

Intraventricular haemorrhage (IVH) is a commonly encountered neurosurgical emergency in most clinical centers. It is most prevalent in cases of hypertensive intracerebral haemorrhage (ICH) with extension into the ventricular system. The most common location for ICH is the striate body (putamen, lenticular nucleus, internal capsule and globus pallidus). This consists of the location of 50% of hypertensive ICH (Hamada *et al.*, 2008). The next common location is the thalamus, which consists of 15%. Following an order of reducing frequency, subsequent locations would be pons, cerebellum, and white matter of cerebrum and finally followed by brainstem.

Due to the anatomical proximity of the basal ganglia structures and thalamus with the ventricular system, most the hemorrhages will rupture thru the ventricular wall into the ventricular system and producing IVH. This occurs in almost 55% of cases. Many studies done previously have shown that the volume of IVH, presence of hydrocephalus, age and admitting GCS are among the predictors for mortality and functional outcome.

CHAPTER ONE: INTRAVENTRICULAR HAEMORRHAGE (IVH)

1.1 Definition and pathogenesis of intraventricular haemorrhage

Intraventricular haemorrhage denotes the presence of blood within the ventricular system of the brain. Intraventricular haemorrhage can be classified into primary or secondary types. Primary intraventricular hemorrhages are confined to the ventricular system and immediate parenchymal lining of the ependymal cells. Thus this bleed originates from intraventricular source or from a lesion that has very close proximity with the ventricular system. These consist of 30% of all cases of intraventricular hemorrhages (Anzai *et al.*, 2000). Some of the common etiological factors that lead to primary intraventricular haemorrhage are head injury, arteriovenous malformation (AVM), aneurysmal bleed and presence of coagulopathy.

Secondary intraventricular haemorrhage, on the other hand, originates as an extension of an intraparenchymal or subarachnoid haemorrhage into the ventricular system. These types of hemorrhages consist of 70% of all cases of intraventricular haemorrhage. Common causes of secondary IVH are hypertensive bleed (especially from the basal ganglia and thalamus), arteriovenous malformation (AVM), coagulopathy, vasculitic bleed, hemorrhagic transformation of ischemic infarct and tumours. It has been reported that the occurrence of IVH in cases of intracerebral or cerebellar haemorrhage significantly increases the rate of mortality.

1.2 Epidemiology of intraventricular haemorrhage

Intraventricular haemorrhage is a common sequelae in patients with intracerebral haemorrhage (ICH). The most common location of bleed that causes extension into the ventricular system is the thalamus. Among all the cases of intracerebral haemorrhage, thalamic ICH is seen in 10-15% of cases (Chen *et al.*, 2011a). The most common location for the occurrence of spontaneous intracerebral bleed is striate body, seen in up to 50% of patients (Hamada *et al.*, 2008). Intraventricular haemorrhage is frequently encountered in patients with thalamic bleed because of its anatomical proximity to the third ventricle. 15-40% of patients with intracerebral haemorrhage will develop intraventricular haemorrhage (Ogura *et al.*, 2006). Simple comparison among patients who have intracerebral haemorrhage with or without intraventricular extension suggests that mortality substantially increased in those with intraventricular involvement. The mortality rate of intracerebral bleed patients is 20-30%, and significantly increases to 50-80% when intraventricular extension is present (Staykov and Schwab, 2013). The presence of intraventricular hemorrhage is also associated with less than 20% good functional outcome as measured by the 90 and 180-day modified Rankin scale (Rathor *et al.*, 2012).

The demographic pattern and data among Malaysian patients with intraventricular haemorrhage has not been previously studied. The study and analysis of functional outcome, morbidity and mortality among local population is challenging, as we are lacking the comprehensive database needed for such an analysis.

1.3 Risk factors for intraventricular haemorrhage

Intraventricular haemorrhage is commonly seen in patients with intracerebral bleed, or known as haermorrhagic stroke. Intraventricular haemorrhage is rarely seen as a primary event, and almost always associated with presence of bleeding in another part of the brain. Therefore, to study the risk factors of intraventricular haemorrhage, it is usually associated with the risks of intracerebral haemorrhage.

Generally, stroke can be categorized as ischemic or haermorrhagic. Ischemic stroke is more common with occurrence rate of 87%, and the remaining 13% constitutes haermorrhagic stroke (Kamikawa *et al.*, 2001). This category of patients share similar risk factors to chronic vascular disease, namely age, hypertension, diabetes, hypercholestremia and cigarette smoking. Risk factors for stroke can be categorized into modifiable and non-modifiable risk factors. Non-modifiable risk factors are increasing age, male sex, family history of stroke and ethnicity. Modifiable risk factors include hypertension, diabetes mellitus, coronary heart disease, hyperlipidemia, obesity, atrial fibrillation, high dietary salt intake, cigarette smoking and alcohol abuse (MOH, 2011a).

The incidence of intracerebral haemorrhage increases significantly after the age of 55 years and doubles with each decade of age until age more than 80 years, where is incidence is 25 times that during the previous decade. The relative risk for age more than 70 years is 7. The relative risk of occurrence of intracerebral haemorrhage with alcohol consumption depends on the period of consumption with the amount consumed. In patients with alcohol consumed within 24 hours, the relative risk of

intracerebral haemorrhage is 4.6 if the amount consumed is 41-120 gm EtOH and the risk escalates to 11.3 if more than 120 gm EtOH is consumed. For consumption period of 1 week prior to the onset of intracerebral haemorrhage, the relative risk is 2 for average alcohol consumption of 1-150 gm EtOH, 4.3 if amount consumed is 151-300 gm EtOH and 6.5 if more than 300 gm EtOH is consumed in that week (Gill *et al.*, 1991).

In Malaysia, diabetes mellitus and hypertension are the two main risk factors of strokes. The Fourth National Health and Morbidity survey in 2011 documented an increasing trend in risk factors for stroke. As many as 32.7 percent of Malaysians (5.8 million of the population) above the age of 18 years suffered from hypertension, a two-fold rise within a period of 10 years. The prevalence of diabetes in Malaysia was noted to be 15.2%, (2.6 million of population), and obesity is at 15.1%. Data recorded in 2006 showed that smoking prevalence in Malaysia was 23.1% among adults (MOH, 2011b). This increasing prevalence, particularly among younger population age group increases the risk of development of artherothrombotic vascular disease, predisposing to younger age onset of stroke.

Other causes of intraventricular haemorrhage consist of tumoural bleed, ruptured cerebrovascular aneurysm, bleeding from arteriovenous malformation (AVMs), post head injury, presence of coagulopathy, haemorrhagic transformation of ischemic stroke, and vasculitic bleed.

1.4 Pathophysiology of intraventricular haemorrhage

Intraventricular haemorrhage occurs when the clot ruptures into the cerebral ventricular system thru the ependymal cell lining or as an extension of subarachnoid haemorrhage. The amount of blood that will be present depends on the balance between the coagulation cascade and the fibrinolytic pathway, which affects the amount of clot formation and dissolution of thrombus.

1.4.1 The coagulation and fibrinolytic system

Blood coagulation and fibrinolysis are initiated and modulated by compounds embedded in the external membrane of cells (tissue factor, thrombomodulin), deposited in extracellular matrix (heparin sulfate, dermatan sulfate, protease), or secreted by vascular cells in a regulated manner (von Willebrand factor, plasminogen activators, and plasminogen activator inhibitors). The hemostatic cascade is based upon the waterfall hypothesis of Ratnoff & Davies who published the sequence of proteolytic reactions starting with factor XII (Hageman factor) activation and ending with formed thrombin proteolyzing fibrinogen to form a clot (Ratnoff, 1988).

Further in the mid-1970s, the cofactor for factor XII activation, prekalikrein and high-molecular-weight- kininogen were identified and deficiencies of these proteins were not associated with a bleeding state (Saito *et al.*, 1975). In 1977, Osterud and Rappaport recognized that factor VIIa is able to activate factor IX to factor IXa (Osterud and Rapaport, 1977). Later, Broze and colleagues recognized that the kinetics of tissue factor pathway inhibitor (TFPI) were such that under physiologic circumstances the factor VIIa–tissue factor complex cannot directly activate factor X but has to go through factor IX activation (Broze, 2003). These latter two studies

indicate the important role of the factor VIIa–tissue factor pathway for physiologic hemostasis.

A key remaining question was how does factor XI, whose deficiency is associated with bleeding, become activated under physiologic circumstances. In 1991, Gailiani and Broze found that formed thrombin can activate factor XI, resulting in amplification of the coagulation system under stress (Badimon *et al.*, 1991). Presently, physiologic hemostasis is believed to be an interacting system of activation and amplification of several zymogens that become serine proteases. The initiator of physiologic hemostasis is factor VIIa when bound to its cofactor tissue factor. Regulation of expression of tissue factor provides a major modulation of physiologic hemostasis. Thrombin in turn amplifies the process by activating factor XI, leading to additional factor IX activation.

The fibrinolytic system's role is to lyse clot formed by thrombin. The anticoagulation system's role is to regulate all the enzymes of the coagulation and fibrinolytic systems so that there is no inappropriate excess of clotting or bleeding.

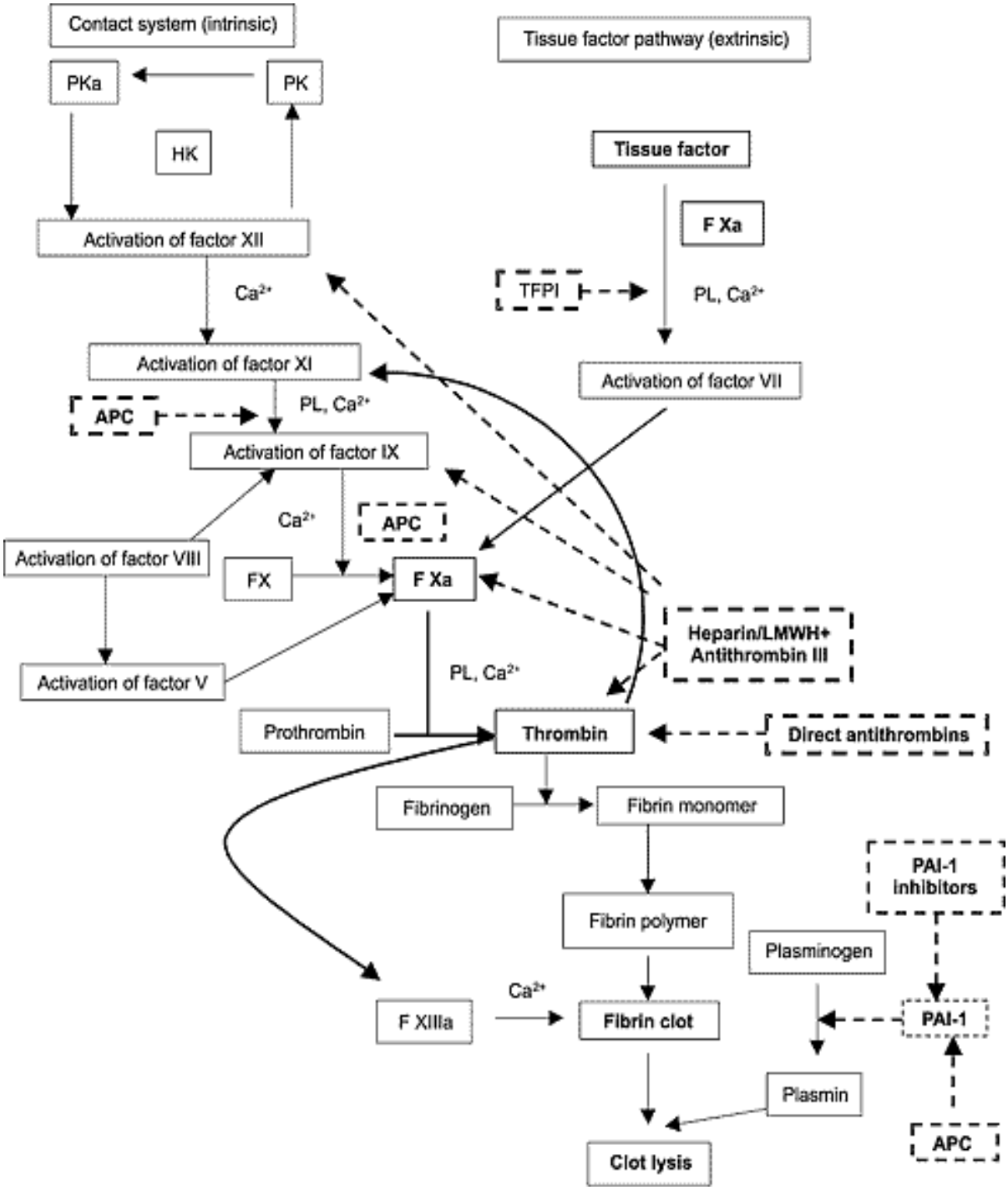

Figure 1.1: Coagulation and fibrinolytic system pathway with all the related clotting factors, cofactors and chemical molecules that can cause alteration in the pathway

1.4.2 Cerebral ventricular system

The cerebral ventricular system provides a low-pressure pathway for the movement of cerebrospinal fluid. This system is frequently broken into when blood at near-systolic pressure passes thru a defect in the arterial wall, forming spontaneous intracerebral haemorrhage as it dissects the brain tissue (Qureshi *et al.*, 2001). Cerebral haemorrhage can occur from defects in the vessel wall, such as aneurysms, arteriovenous malformation, vasculitic, impaired coagulation profile and hypertensive bleed. Therefore, multiple different diseases are capable of producing collection of blood that may occlude or obstruct the intraventricular space. Bleeding at the deep intracranial sites near to the ventricles leads to early intraventricular rupture and leads to sudden increase of intracranial pressure. This is commonly seen in thalamic or caudate nucleus haemorrhage. As for bleeding that occurs at sites that are further away from the ventricles will form clots and gradually accumulates and the increasing haemorrhage size produces rupture into the ventricular system.

The actual rupture is often associated with reduced conscious level and can be recognized clinically. The subsequent sequelae is usually death if the condition is not intervened. The main aim of intervention is for rapid removal of clot and ICP monitoring which is aimed at moving the intraventricular haemorrhage from pathological domain into the clinical domain, which allows for qualitative and quantitative measurement of the pathology.

1.4.3 Clinical pathophysiology of intraventricular haemorrhage

The clinical pathophysiology of intraventricular haemorrhage is described on how this neurosurgical condition leads to clinical outcome, morbidity and mortality. Intraventricular haemorrhage contributes to morbidity in 3 main ways (Hanley, 2009). Firstly, when haemorrhage occurs into the ventricular system, it will organize to form clots and will block the narrow parts of the ventricular conduits and hence produces acute hydrocephalus. If left untreated, acute hydrocephalus can cause elevation of the intracranial pressure, can progresses to death.

At present, the management of IVH with presence of hydrocephalus entailed the placement of one or more external ventricular drainage for drainage of blood and CSF from the ventricular system and normalization of intracranial pressure. However, this approach alone may not be sufficient in improving the outcome of patients with IVH. One of the common problems encountered is to maintain the patency of the ventricular catheters. The catheters can be blocked easily by the blood clots and hence will defy the purpose of maintaining the intracranial pressure.

Clinically, controlling ICP does not usually improve the patient immediately. Thus, direct mass effect from the IVH may be another significant pathophysiologic event independent of ICP elevation. This may suggest that placing an external ventricular catheter alone may not be sufficient as the mass effect from the blood clot may still persist after this procedure. Due to these issues, additional measures such as performing an endoscopic washout for patients with IVH prior to the placement of external ventricular drainage have been studied.

Secondly, the prolonged presence of clot deep within the brain is related to reduced level of consciousness and mortality. EVD does not consistently improve either event. This is because drainage alone does not alter the size of ventricles, brain tissue edema, and the inflammation provoked by the presence of intraventricular blood, and it does not increase the rate of blood clot resolution. To worsen the situation, placement of a drain is frequently complicated by infection such as meningitis and ventriculitis, and it also contributes to formation of new haemorrhage (Jernigan *et al.*, 2014).

Thirdly, the blood degradation products will flow via the CSF pathways to the arachnoid granulations. Prolonged contact of the blood breakdown products with the arachnoid granulations will lead to an inflammatory respond that permanently scars the granulations and causes delayed communicating hydrocephalus. When this condition occurs, the patient will require placement of a shunt for CSF diversion.

It is still debatable whether by performing an endoscopic washout, it will prevent the damage of arachnoid granulations by blood degradation products and hence will not make the patient shunt dependent. However, there are not many studies done up-to-date to establish and complement these findings. There are also no data available for the local population.

1.5 Clinical presentation of intraventricular haemorrhage

The signs and symptoms of patients who present intraventricular haemorrhage can be generalized or focal. General symptoms are characterized by headache, nausea, vomiting, giddiness, loss of consciousness, and generalized seizures. These symptoms occur due to the sudden increase in intracranial pressure. As for the focal signs and symptoms, the clinical presentation depends on the location of the lesion, and on which neurovascular structures that are damaged.

For patients who have intraventricular haemorrhage as an extension from cortical bleed, they present with transient ischemic attack (TIA) like symptoms in 50% of cases (Qureshi *et al.*, 2001). However, unlike the typical TIAs, there is usually numbness, tingling sensation of the limbs, and progressively worsening weakness, in which either the upper or lower limbs are more affected than the other. The weakness and numbness progresses in a manner similar to a Jacksonian march pattern, corresponding to the motor and sensory homunculus. It may also spill over vascular territories, which is rather an electrical phenomenon rather than an ischemic or haemorrhagic event.

The focal symptoms of patients with lobar haemorrhage with intraventricular extension depend on the involved lobe. Frontal lobe haemorrhage usually presents with frontal headache with contralateral hemiparesis, usually in the arms with mild weakness on the face and lower limb. The patient may also have frontal lobe syndrome, based on with part of the frontal lobes are affected. Parietal lobe involvement leads to contralateral hemisensory deficit with mild hemiparesis. When haemorrhage occurs in the occipital lobe, patient usually presents with ipsilateral eye

pain and contralateral homonymous hemianopia. Temporal lobe haemorrhage on the dominant hemisphere causes fluent dysphasia, with poor auditory comprehension but with relatively good repetition.

Patients with putaminal haemorrhage, which the most common location for the development of spontaneous intracerebral haemorrhage, there will be smooth gradual deterioration in 62% of patients and the symptoms, are never fluctuating. The remaining 38% of patients presents with maximal neurological deficit at onset of ictus (Nagaratnam *et al.*, 2001). Contralateral hemiparesis may progress to hemiplegia or even coma and death. Headache is seen in 14% of patients with putaminal haemorrhage, and 72% does not have headache at any time of the disease. Papilledema and subhyaloid preretinal haemorrhages are rarely present.

As for patients with thalamic haemorrhage with intraventricular extension, the classical initial presentation is hemisensory loss, as thalamus is the main relay station for sensory modalities. When there is compression or extension of the bleed into the internal capsule, hemiparesis can occur. The hemiparesis is similar to putaminal haemorrhage type, but the contralateral sensory loss is striking and widespread. Extension into the upper brainstem (midbrain and upper pons) can also occur, and patient presents with vertical gaze palsy, convergence retraction nystagmus, skew deviation, loss of convergence, ptosis, miosis and anisocoria. Headache is observed in 20-40% of patients with thalamic haemorrhage. Extension into the ventricular system is common in thalamic bleed, because of the anatomic proximity.

On the other hand, patients with cerebellar haemorrhage presents initially with signs and symptoms of increased intracranial pressure, the the compliance volume in the posterior fossa is small ($15cm^3$) and obstructive hydrocephalus occurs early as a result of the 4^{th} ventricle compression. Hydrocephalus can also result from the extension of the cerebellar haemorrhage into the ventricular system resulting in intraventricular haemorrhage. In addition to that, the patient may also present with signs and symptoms of direct brainstem compression. When the facial colliculus at the floor of 4^{th} ventricle is compressed, the patient presents with facial nerve palsy. Further worsening of the compression leads to loss of consciousness and comatose state due to the dysfunction of ascending reticular activating system (ARAS) fibers.

Delayed deterioration after initial haemorrhage is usually caused by rebleeding (early or late), worsening of cerebral edema, hydrocephalus or seizures. Early rebleeding occurs within 24 hours from the onset of initial ictus. This is seen more commonly in patients with basal ganglia haemorrhage, and less common in lobar haemorrhages. The incidence of hematoma enlargement decreases with time, 33-38% in 1-3 hours, 16% in 3-6 hours, and 14% within 24 hours. Patients with enlarging hematoma more likely to have presented with a large hematoma or has presence of coagulopathy. Late rebleeding from an initial intracerebral haemorrhage ranges from 1.8-5.3%, depending on the length of follow-up (Arakawa *et al.*, 1998). Diastolic blood pressure was significantly higher in the group with recurrent haemorrhage with a 10%/year risk for DBP > 90mmHg versus less than 1.5%/year risk for DBP < 90mmHg. Other risk factors include diabetes, cigarette smoking and alcohol abuse. Recurrent haemorrhage may also indicate underlying vascular malformations or amyloid angiopathy.

Presence and worsening of edema and ischemic necrosis around the haemorrhage can also cause delayed deterioration. Although necrosis from mass effect of the clot contributes to a small part to the edema itself, the mass effect is insufficient to account for the amount of edema that occurs. The edema is caused by the release of edemogenic toxin as the clot is degraded (Badimon *et al.*, 1991). Experiments with various components of blood clots have revealed that thrombin released from the clot causes increased permeability of the blood brain barrier and it is also a potent vasoconstrictor, which can worsen the ischemia.

1.6 Imaging modalities in intraventricular haemorrhage

Imaging plays an important role in the diagnosis and management of patient with intraventricular haemorrhage. The role of imaging is (1) to establish the diagnosis of intraventricular haemorrhage, as evidenced by presence of hyperdensity within the ventricular system, (2) to determine if the intraventricular haemorrhage is primary or secondary extension from another origin of clot, (3) to confirm presence of hydrocephalus and its degree of severity, (4) to objectively quantify clot volume, midline shift and patency of basal cisterns.

The most common imaging modality that is performed is computed tomography (CT) scan. It remains the imaging modality of choice for the primary evaluation of intraventricular haemorrhage, as it is widely available in most hospitals 24 hours a day, is fast, reliable and safe. The objective of non-enhanced CT scan is similar with the role of imaging as mentioned above.

Typical appearance of intraventricular haemorrhage on CT scan is an area of hyperdensity within the ventricular system. In cases of secondary intraventricular haemorrhage, the location of the primary bleed can be visualized and the clot volume (Kothari *et al.*, 1996) and extent of mass effect can be objectively calculated. (Figure 1.1, 1.2)

Magnetic resonance imaging (MRI) is usually not the procedure of choice for the initial study as it is not available in all hospitals. However, MRI is more sensitive than CT to very small amounts of blood, especially in the posterior fossa, where CT images are distorted by bony artifact. Both FLAIR and SWI sequence (especially at 3 Tesla) are sensitive to small amounts of blood. Especially the latter will demonstrate tiny amounts of blood pooling in the occipital horns, and resulting in susceptibility induced signal drop out (Sohn *et al.*, 2005).

On FLAIR the signal intensity will vary depending on the timing of the scan. Within 48 hours blood will appear as hyper-intense to the attenuated adjacent CSF. Later the signal is more variable and can be difficult to distinguish from flow related artifact (particularly in the third and fourth ventricles) unless other sequences are also used.

Some of the disadvantages of MRI are imaging cost that is significantly higher than CT scanning. It is also difficult to ventilate and access patient during MRI as all the equipment must be compatible with the MRI scanner. The scanning time is also longer with MRI and it requires specialized interpretation of findings. Patient factors such as claustrophobia, cardiac pacemaker and metal implants also need to be considered.

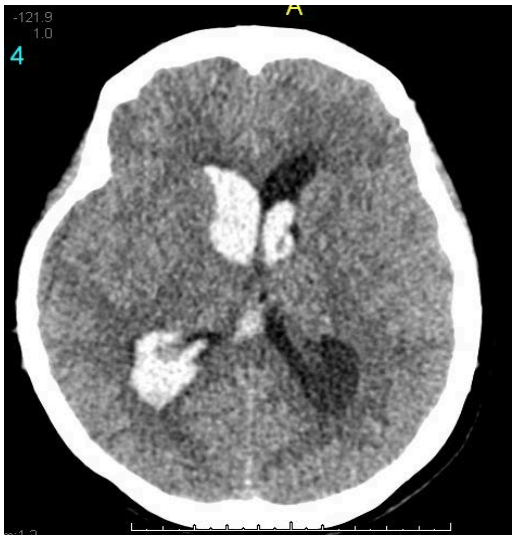

Figure 1.2: CT findings of primary intraventricular haemorrhage, the hematoma is confined to the ventricular system

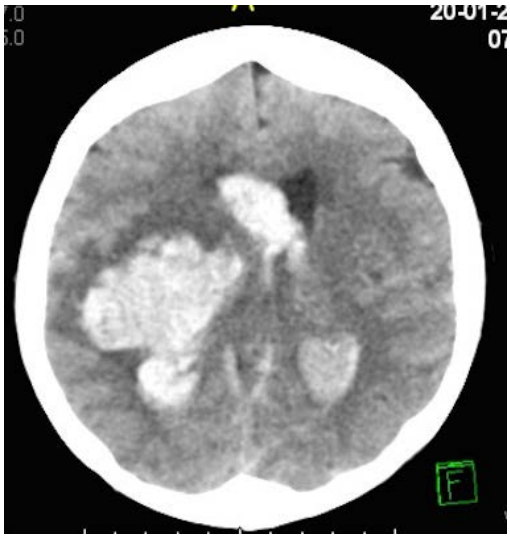

Figure 1.3: CT findings of secondary intraventricular haemorrhage as an extension of right basal ganglia bleed

1.7 Scoring system for intraventricular haemorrhage

As with any other intracranial pathology, there is an objective system to score the severity of intraventricular haemorrhage. At present, there are two widely acceptable grading systems in the literatures, which are Graeb grading & LeRoux grading (Graeb *et al.*, 1982). In Graeb grading of intraventricular haemorrhage, the score ranges from 2-12. The score is a product of addition of the component scores that is given to the lateral ventricles, 3rd and 4th ventricles. Presence of blood in the lateral ventricles are given score of 1 if there is only traces of blood, 2 if less than ½ of ventricle filled with blood, 3 if more than ½ is filled with blood and 4 when the ventricles are filled with blood and expanded. As for the 3rd and 4th ventricles, score 0 is given when there are no blood in the 3rd and 4th ventricle, score of 1 indicates that blood is present, but the

ventricle size is normal and score of 2 is given when the 3rd and 4th ventricles are filled with blood and expanded.

As for the LeRoux grading, all the ventricles are scored evenly, from 1-4 and then each of the component scores are added to get the final result. Score of 1 is given when there are only traces of blood, 2 if only less than ½ the ventricles are filled with blood, 3 if more than ½ is filled with blood and 4 when the ventricles are filled with blood and expanded (LeRoux *et al.*, 1992). Any score of more than 6, obtained via the Graeb or Le Roux grading system is defined as massive intraventricular haemorrhage.

The presence of hydrocephalus in patients with intraventricular haemorrhage is commonly seen, as the blood clot causes blockage to the normal CSF pathways. To grade the severity of hydrocephalus, Diringer has formulated a scoring system, which scores the lateral ventricle, 3rd and 4th ventricles. As for the lateral ventricles, it is further scored in 3 different locations (frontal horn, atrium and temporal horn). Each of these component is given score of 0-3, in which 0 represents normal shape of the ventricle, 1 mean mild hydrocephalus, 2 for moderate and 3 when there is rounding of the ventricular wall or presence of sulcal effacement. The maximum score for the Diringer grading of hydrocephalus is 24 (Diringer *et al.*, 1998).

Table 1.1 Graeb grading system for intraventricular haemorrhage (Graeb *et al.*, 1982)

Location of clot	Trace of blood	Less than 50% filled	More than 50% filled	Completely filled and expanded
Lateral ventricles	1	2	3	4
Location of clot	No blood present	Blood present, ventricle normal size	Filled with blood and expanded	_
3rd ventricle	0	1	2	_
4th ventricle	0	1	2	_

* The total score is the addition of both lateral ventricles score, 3rd ventricle score and 4th ventricle score (Score range 2-12)

Table 1.2 Le Roux grading system for intraventricular haemorrhage (LeRoux *et al.*, 1992)

Location of clot	Trace of blood	Less than 50% filled	More than 50% filled	Completely filled and expanded
Lateral ventricles	1	2	3	4
3rd ventricle	1	2	3	4
4th ventricle	1	2	3	4

* The total score is the addition of both lateral ventricles score, 3rd ventricle score and 4th ventricle score (Score range 4-16)

Table 1.3 Diringer grading system for hydrocephalus (Diringer *et al.*, 1998)

Score	0	1	2	3
Frontal horn	No	Mild	Moderate	Rounding, sulcal effacement
Atrium	No	Mild	Moderate	Rounding, sulcal effacement
Temporal horn	No	Mild	Moderate	Increased width
3rd ventricle	No	Mild	Moderate	Ballooning
4th ventricle	No	Mild	Moderate	Ballooning

* Score range 0-24

1.8 Treatment options for intraventricular haemorrhage

The treatment option for intraventricular haemorrhage is directed towards the removal of blood clots and cerebrospinal fluid from the ventricular system in order to normalize intracranial pressure. Generally, the management options that are available includes (1) placement of external ventricular drainage (EVD) catheters,
(2) conventional craniotomy and clot evacuation, (3) external ventricular drainage with adjunctive thrombolytics and (4) endoscopic washout of the intraventricular haemorrhage.

Traditionally, the treatment of intraventricular haemorrhage has entailed the placement of one or more external ventricular drains to allow blood clots and cerebrospinal fluid to flow out from the ventricles. This will lead to normalization of the intracranial pressure. However, this approach alone is often not sufficiently effective in improving the poor prognosis of massive intraventricular haemorrhage (Onem *et al.*, 2007). External ventricular drains only address one of the acute consequences of intraventricular haemorrhage, which is acute obstructive

hydrocephalus. The catheter often becomes occluded because of thick blood clots, and results in failure of drainage (Kiymaz *et al.*, 2005). When this happens, the conventional therapy is removal of the occluded catheter and insertion of a second catheter in another location, preferably one that is free of blood. Relocation of the external ventricular drain carries a low but clinically significant risk of intracerebral haemorrhage, and is often unsuccessful as the drain can reliably access only a portion of the ventricles. If the accessible portion is occupied by blood, then the newly placed external ventricular drain will likely occlude.

For many patients, drainage is unsuccessful and they succumb to obstructive hydrocephalus. Even when drainage is successful, persistent blood clots increase the time that drainage is needed, thus increasing the risk of ventriculitis, which is about 16% when blood is in the ventricle (Fabiano *et al.*, 2013). At least three factors are associated with increased risk of ventriculitis: presence of blood within the ventricular system, duration of catheterization, and irrigation of the external ventricular drainage system (Lozier *et al.*, 2008).

External ventricular drainage alone does not alter the rate of intraventricular clot resolution or impact the effect of blood on deep periventricular brain tissue edema generation and the accompanying progressive cell death. External ventricular drains cannot remove the blood clot, relieve local tissue compression from distended ventricles, or alter the rate of blood clot resolution (Naff *et al.*, 2001). It also does not shorten the time that the blood clot is in contact with the ventricular system and deep brain structures.

Although the placement of external ventricular drain is helpful in controlling increased intracranial pressure, the blood clots must be cleared from the cerebrospinal fluid conduits by the patients' own fibrinolysis mechanism. Furthermore, external ventricular drains fails to decrease the degree and incidence of communicating hydrocephalus, because it does not hasten the resolution of the intraventricular blood clot which leads to the pathomechannics of the development of communicating hydrocephalus. Delayed communicating hydrocephalus is caused by an inflammatory reaction generated by fibrin degradation products, which is formed during clot resolution. This will render the patient drainage dependent and requires surgery for shunt insertion, leaving the patient with lifelong risk of shunt infection, malfunction and occlusions (Li *et al.*, 2013).

Another potential treatment modality is surgical evacuation of clot via conventional craniotomy, which is mainly performed in patients with intracerebral haemorrhage. Surgical craniotomy with clot evacuation has been shown to increase the percentage of intracerebral haemorrhage volume reduction in the first 24 hours when compared with best medical therapy (76% versus 0%). However, craniotomy has not been shown to improve the 30-day outcome as measured by Glasgow Outcome Scale when compared with best medical therapy (Zuccarello *et al.*, 1999). With regard to intraventricular haemorrhage, standard craniotomy and clot evacuation has several limitations. Firstly, complete surgical removal of the blood clot is hazardous and even impossible if it involves all the ventricles. Secondly, craniotomy is a major surgery and associated with high morbidity rate. Third, surgery may worsen the cerebral edema and hence lead to increased intracranial pressure.

Therefore, with these risks and benefits in mind, the best management should not be as conservative as an external ventricular drain placement, nor shall it be as aggressive as a conventional craniotomy and clot evacuation. These has raised interest in the utilization of neuroendoscopy for ventricular clot evacuation and hence reduction in the intracranial pressure. Massive intraventricular haemorrhage requires aggressive and rapid management to reduce the intracranial hypertension. The amount of intraventricular blood is a strong prognostic factor, in terms of morbidity and mortality. Therefore, fast removal of the clot should be considered a priority.

1.9 Outcome following intraventricular haemorrhage

The outcome of patient with intraventricular bleed is predicted by its severity at presentation. If untreated, the mortality rate of patients with intraventricular haemorrhage ranges from 50% to 80%. In patients who undergo surgical management (external ventricular drainage or endoscopic washout) the 30 and 90-day mortality rate is 12.5% and 20.8% respectively, with no significant difference between the 2 groups. Patient factor such as age and initial GCS on arrival has significant impact on the functional outcome, as measured by modified Rankin scale.

CHAPTER TWO: BACKGROUND OF STUDY

2.1 External ventricular drainage for intraventricular haemorrhage

The placement of one or more external ventricular drains to allow blood clots and cerebrospinal fluid to flow out from the ventricles. This will lead to normalization of the intracranial pressure. However, this approach alone is often not sufficiently effective in improving the poor prognosis of massive intraventricular haemorrhage (Basaldella *et al.*, 2012). External ventricular drains only address one of the acute consequences of intraventricular haemorrhage, which is acute obstructive hydrocephalus. The catheter often becomes occluded because of thick blood clots, and results in failure of drainage.

For many patients, drainage is unsuccessful and they succumb to obstructive hydrocephalus. Even when drainage is successful, persistent blood clots increase the time that drainage is needed, thus increasing the risk of ventriculitis, which is about 16% when blood is in the ventricles (Fabiano *et al.*, 2013). At least three factors are associated with increased risk of ventriculitis: presence of blood within the ventricular system, duration of catheterization, and irrigation of the external ventricular drainage system (Lozier *et al.*, 2008).