SURVIVAL ANALYSIS AND FUNCTIONAL OUTCOME AT 6 MONTHS IN SURGICAL TREATMENT OF SPONTANEOUS SUPRATENTORIAL INTRACEREBRAL HEMORRHAGE (ICH).

By

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To,

My Parent, My Wife and family
For their patience.

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CONTENTS

Lists of Tables and Figures.

Figure	Page

ABSTRAK

Bahasa Malaysia.

Topik: Analisa Hayat dan Kesan Akhir Rawatan Pembedahan bagi Pesakit Perdarahan Intraserebral Spontan.

Objektif.

Matlamat penyelidikan ini ialah untuk menilai peranan rawatan pembedahan bagi perdarahan intraserebral spontan dan mengenalpasti factor-faktor radiologi, genetik, biokemikal dan rawatan di dalam menentukan jangka hayat dan kesan akhir rawatan.

Prosedur Kajian.

Kajian ini ialah kajian prospektif kohot, termasuk pesakit yang mengalami perdarahan intraserebral spontan yang menepati kriteria untuk rawatan pembedahan. Kajian ini dijalankan untuk tempoh 13 bulan, dari Februari 2004 sehingga Mac 2005.Rawatan pembedahan ini dilakukan secara kaedah kraniotomy dan teknik mikrosurgeri dan bagi sesetengah kes, kaedah kraniektomi dekompresif.Ventrikulostomi untuk mengukur tekanan otak dan mengeluarkan darah, kajian pengaliran darah otak dan mikrodialisis untuk pengukuran tahap laktat:pyruvat dijalankan untuk setiap pesakit. Kajian habungkait diantara Apolipoprotein E ε4 dan kesannya keatas pesakit juga dilakukan. Pengukuran akhir kajian ini ialah jangka hayat dan kesan akhir rawatan berdasarkan kepada 'Glasgow Outcome Scale' (GOS). GOS I-III didefinasikan sebagai kesan akhir yang tidak baik dan GOS IV-V didefinasikan sebagai kesan akhir yang baik. Faktor-faktor klinikal, radiologikal, genetik, biokemikal dan rawatan yang menentukan jangka hayat pesakit dan pencapaian fungsi dianalisa bagi mengenalpasti factor yang signifikan. Analisa univariat bagi factor-faktor kajian dan 'GOS' pada masa 6 bulan dilakukan dengan kaedah 'chi-square' dan analisa kesan hayat menggunakan ujian 'Kaplan Meier' dan 'log-rank'. Bagi analisa multivariat, kaedah

'binary logistic regression' digunakan untuk kesan akhir rawatan dan 'Cox regression' untuk kesan hayat.

Keputusan.

36 pesakit telah terlibat didalam kajian bagi tempoh diantara bulan Februari 2004 dan Mac 2005. Perkembangan semua pesakit dilihat untuk tempoh 6 bulan. Kajian ini mempunyai 19 pesakit lelaki and 16 pesakit perempuan yang berumur diantara 39 dan 76 tahun dengan purata umur 58.6 tahun .Sebanyak 27 (75%) pesakit mempunyai 'Glasgow Coma Score' diantara 5 ke 8 dan 9 (25%) pesakit mempunyai 'Glasgow Coma Score' 9. Tempoh hayat pesakit didalam kajian adalah diantara 2 ke 180 hari, dengan purata 105.36 ± 76.4 hari. Pada tempoh 6 bulan, 20 (55.6%) pesakit mempunyai GOS I, 1 (2.8%) pesakit mempunyai GOS II, 10 (27.7%) pesakit mempunyai GOS III dan 5 (13.9%) pesakit mempunyai GOS of IV. Tiada pesakit didalam kajian mempunyai GOS V. Kadar kematian pada 6 bulan ialah 55%. 86% pesakit mendapat kesan akhir yang tidak baik (GOS I-III) dan 14% mendapat kesan akhir yang baik (GOS IV-V). Kajian Apolipoprotin E menunjukkan tiada pesakit mempunyai allel APOE ε4.Didalam analisa univariat untuk menentukan pencapaian fungsi pada masa 6 bulan berasaskan kepada 'GOS' menunjukkan 3 variabel yang signifikan iaitu 'anjakan tengah' (p=0.009), 'pengaliran setempat serebral'(p=0.034) dan 'status trakeostomi'(p=0.047). Analisa univariat untuk jangka hayat menunjukkan 'pengaliran setempat serebral'(p=0.0143), 'anjakan tengah'(0.0064) dan status pupil (p=0.0016) pesakit adalah 3 faktor yang signifikan dalam menentukan jangka hayat. Variabel-variable yang terpilih ini akan dimasukkan ke dalam analisa 'binary logistic regression' dan analisa 'Cox regression' untuk menentukan factor yang paling signifikan dalam kesan akhir rawatan dan jangka hayat. Anjakan tengah dikanalpasti sebagai factor signifikan didalam menentukan kesan akhir rawatan pada 6 bulan

(OR=20.8; 95% CI = 1.90-227.26; p=0.013), dan status pupil dikenalpasti sebagai factor penting didalam menentukan kesan hayat (HR = 2.298; 95% CI 1.168 – 4.523; p=0.016). Pesakit yang mempunyai anjakan tengah > 5 mm mempunyai 21 kali kemungkinan untuk mendapat kesan akhir yang tidak baik (GOS I-III) dan pesakit yang mempunyai pupil yang tidal normal mempunyai risiko kematian sebanyak 2.3 kali jika dibandingkan dengan pesakit yang mempunyai pupil yang normal.

Kesimpulan.

Rawatan pembedahan untuk pesakit intraserebral hanya memberi faedah kepada sebilangan kecil pesakit dimana 14% mendapat pencapaian fungsi yang baik dan 86% pesakit mendapat pencapaian fungsi yang tidal baik. Pesakit yang mempunyai anjakan tengah > 5 mm mempunyai 21 kali kemungkinan untuk mendapat kesan akhir yang tidak baik (GOS I-III) dan pesakit yang mempunyai pupil yang tidal normal mempunyai risiko kematian sebanyak 2 kali ganda jika dibandingkan dengan pesakit yang mempunyai pupil yang normal.

ABSTRACT

Title: Survival Analysis and Functional Outcome at 6 months in Surgical Treatment of Spontaneous Supratentorial Intracerebral Hemorrhage (ICH).

Objectives.

The aim of this study is to evaluate the role of surgery in patients with spontaneous supratentorial intracerebral hemorrhage and to identify predictors of outcome and survival including radiological, genetic, biochemical and treatment factors.

Study design and method.

This is a prospective cohort study, involving patients with spontaneous supratentorial intracerebral hemorrhage, who fulfill the inclusion criteria for surgical evacuation of the hematoma. This study was conducted over a 13 month period, from February 2004 to March 2005.Surgery consisted of evacuation of hematoma using craniotomy and microsurgical techniques, as well as in some cases, a decompressive craniectomy. The ventriculostomy for intracranial pressure monitoring and drainage and regional cortical cerebral blood flow (rCoBF) monitoring and microdialysis were performed in all subjects. In addition, the association between Apolipoprotein E (APOE) ε4 and outcome was also studied. The study end points were survival time and functional outcome at 6 months based on a dichotomised Glasgow Outcome Scale (GOS). GOS of 1-3 was defined as poor or unfavorable outcome and GOS of 4-5 was defined as good or favorable outcome. The selected clinical, radiological, genetic, biochemical and treatment factors that may influence the survival and functional outcome were analysed for its significance. The univariate analysis of the relation between various variables and GOS at 6 months were analysed using the chi-square test and the survival time was analysed using the Kaplan Meier and log rank test. In multivariate

analysis, the binary logistic regression for functional outcome and Cox regression analysis for survival function were performed.

Results.

36 patients were recruited into the study during the period of February 2004 and March 2005. All of those were followed-up for a period of 6 months. There were 19 males and 17 females with age ranged from 39 to 76 years and a mean age of 58.6 (±10.1) years and a median age of 61 years. 27(75%) patients had Glasgow Coma Score (GCS) between 5 to 8 on admission and 9(25%) were admitted with GCS of 9 on admission. The survival time ranged from 2 to 180 days with a mean survival time of 105.36 ± 76.4 days. At 6 months, 20 (55.6%) patients had GOS I, 1 (2.8%) patient had GOS II, 10 (27.7%) patients had GOS III and 5 (13.9%) had GOS of IV. None of the patients in this study had GOS of V. The mortality rate at 6 months was 55%. 86 % had a poor or unfavorable outcome (GOS I-III) and 14% had good or favorable outcome (GOS IV-V). The study of Apolipoprotein E showed that the APOE ε4 allele was not detected in all patients. In the univariate analysis for the functional outcome based on GOS, 3 significant variables were identified, the midline shift (p=0.009), regional cortical cerebral blood flow (rCoBF), (p=0.034) and tracheostomy status (p=0.047). The univariate analysis for survival function revealed that the regional cortical cerebral blood flow (rCoBF), (p=0.0143), midline shift (p=0.0064) and pupillary status on admission (p=0.0016) were significant predictors of survival function. The selected variables were then incorporated into models generated by binary logistic regression and Cox regression analysis to identify significant predictors of functional outcome and survival function. Midline shift was the single significant predictor of functional outcome at 6 months (OR=20.8; 95% CI = 1.90-227.26; p=0.013), and the pupillary status was sole significant predictor of survival

function (HR = 2.298; 95% CI 1.168 – 4.523; p=0.016). Patients with midline shift > 5mm has almost 21 times higher chances of being associated with poor outcome (GOS I-III) and patients with abnormal pupil on admission has 2.3 times risk of mortality compared to patients with normal pupillary reaction on admission.

Conclusion.

Surgical treatment for spontaneous intracerebral hemorrhage in this group of patients only benefited a small number of patients in terms of favorable outcome (14%) and in the majority of patients (86%), the outcome was unfavorable. Patients with midline shift > 5mm has almost 21 times higher chances of being associated with poor outcome (GOS I-III) at 6 months and patients with an abnormal pupil on admission had an increase in mortality risk of about 2 times compared to patients with normal pupillary reaction on admission.

1.INTRODUCTION.

Intracerebral hemorrhage (ICH) is bleeding that occurs directly into the brain parenchyma. It is differentiated from intraventricular hemorrhage (IVH) and SAH, which involve bleeding into the brain's ventricular system and subarachnoid space, respectively. Often, ICH is classified as primary (unrelated to congenital or acquired lesions), secondary (directly related to congenital or acquired conditions), and/or spontaneous (not secondary to trauma or surgery). It is a common devastating neurologic event that causes high morbidity and mortality with profound economic complications. Unlike the declining mortality with subarachnoid hemorrhage due to improvements in surgical and critical care techniques, the morbidity and mortality of ICH have remained relatively unchanged throughout the past several decades. The role of medical and surgical treatment in ICH continues to be controversial. Studies of surgical hematoma evacuation in ICH using a variety of methods have yielded either negative or inconclusive results. Likewise, no medical treatment has been shown conclusively to benefit patients with ICH.

This study is the first prospective cohort study in Malaysia assessing the role of surgery in the treatment of spontaneous supratentorial intracerebral hemorrhage in combination with best medical therapy in a selected group of patients meeting the inclusion and exclusion criteria for the study. This study was also conducted to identify associated clinical, radiological, genetic, biochemical and treatment factors that could significantly determine the survival time and functional outcome following surgical therapy for ICH.

The study of Apolipoprotein E for the detection of APOE ε4 allele, cerebral autoregulation test using transcranial Doppler sonography (TCD) and the thigh cuff technique was performed in all subjects on admission to intensive care unit. In some

patients, an applanation tonometry assessing the central systemic haemodynamic by measuring the aortic augmentation index using the Pulse Wave Analysis (PWA) system was done.

All patients in this study underwent an open craniotomy or decompressive craniectomy and hematoma evacuation. In addition, an intraventricular catheter for intracranial pressure (ICP) monitoring and drainage, intracerebral microdialysis catheter for monitoring of brain chemistry using lactate:pyruvate ratio and Saber 2000 cerebral blood flow (CBF) sensor for measurement of regional cortical blood flow (rCoBF) was inserted on the cortical surface in all patients. After the surgery, all patients were admitted to the intensive care unit and a standard medical therapy was provided.

The outcome of interest were dichotomized Glasgow Outcome Scale (GOS) into good or favourable outcome (GOS IV – V) and bad or unfavourable outcome (GOS I, II and III) and the survival analysis based on time to event which is the duration of patient died after intervention.

2.LITERATURE REVIEW.

INTRODUCTION.

Spontaneous supratentorial intracerebral hemorrhage (ICH) is bleeding into the parenchyma of the brain that may extend into the ventricles and in rare cases, the subarachnoid space. Intracerebral hemorrhage (ICH) accounts for 10 to 15 % of all cases of stroke and is associated with disproportionately high morbidity and mortality. It is associated with the highest mortality rate, with only 38% of affected patients surviving the first year.[1] Depending on the underlying cause of bleeding, intracerebral hemorrhage is classified as either primary or secondary. Primary intracerebral hemorrhage, accounting for 78-88% of cases, originates from spontaneous rupture of small vessels damaged by chronic hypertension or amyloid angiopathy.[2] Secondary intracerebral hemorrhage occurs in a minority of patients in association with vascular abnormalities such as arteriovenous malformations and aneurysm, tumors, trauma or impaired coagulation.

EPIDEMIOLOGIC FEATURES.

Incidence.

Intracerebral hemorrhage is common, with an estimated prevalence of 37,000 cases per year in the United States.[3] It is twice as prevalent as subarachnoid hemorrhage (SAH) and accounts for approximately 10% of all strokes. Incidence rates vary on the basis of age, race and demographics. The most recent population-based studies using computed tomography (CT) verification estimate that the overall incidence of ICH is between 12 and 15 cases per 100,000 population.[4]There is a slight male predominance. The incidence of ICH increase exponentially with increasing age, with

rates doubling every 10 years after age 35 years.[5] The overall mean age for patients with ICH is 61 years.

In contrast, ICH is more common in Asian, African and Hispanic American populations. Incidence rates are estimated to be twice as high in this populations.[6] The reason for the large discrepancy among among populations is unclear but probably is accounted for by differences in education, poor control of hypertension, and lack of health care availability. The population-based series from Asia, specifically from Japan which included thousands of stroke cases where hemorrhage accounted for approximately 25% of all strokes, and intraparenchymatous hemorrhage comprised two thirds of the total.[7] In a prospective ASEAN-wide collaboration study of 3,200 hospitalised stroke patients, 22% of all strokes were hemorrhagic.[8] In general, the frequency of hemorrhagic stroke ranges from 17.2% seen in Malaysia[9] to 39% seen in Surabaya, Indonesia.[10] Data for the incidence of hemorrhagic stroke among ASEAN countries is presented in Table 2.1. With respect to our local data, in 1994, the University Hospital Stroke Registry (UHSR) was established at the University Hospital Kuala Lumpur. Out of 413 cases of stroke, 71(17.2%) were due to intracerebral hemorrhage, 85% of patients had a history of hypertension.

Country	Type (Mixed urban and rural)	Hemorrhagic stroke (%)
Malaysia	Hospital based	17.2%
Kelantan	Hospital based	32.9%
Indonesia	Hospital based	38.6%
Singapore	Hospital based	26.0%
Vietnam	Community-wide	30.0%
Thailand	Hospital based	27.4%
ASEAN	Hospital based	22.3%

Table 2.1: The frequency of hemorrhagic stroke in ASEAN countries.

Aetiologies of Spontaneous Intracerebral Hemorrhage.

The etiologies of intracerebral hemorrhage are diverse, complex, and dynamic. Intracerebral hemorrhage secondary to pathologic changes initiated by chronic hypertension is responsible for approximately 75% of all cases of primary ICH.[11] More recent clinical and pathologic series have reported a lower percentage.[12] Cerebral amyloid angiopathy, the next most common cause of primary ICH is distinct from systemic amyloidosis and leads to the infiltration of amyloid protein into the media and adventitia of the cortical arterioles of the brain. Its prevalence increases with age; more than 60% of autopsy samples from patients older than 90 years exhibit some degree of amyloid deposition. Cerebral amyloid angiopathy is estimated to account for more than 20% of all ICH in patients older than 70 years.[13]

Underlying vascular abnormalities such as arteriovenous malformations, cerebral aneurysms, or cavernous angiomas are an important cause of secondary ICH. The exact frequency of their occurrence is difficult to establish but may approximate 5% of all ICH. Vascular abnormalities occur primarily in younger populations, accounting for approximately 38% of ICH in patients younger than 45 years.[14] Bleeding directly

into primary or metastatic brain tumors is another cause of secondary ICH but accounts for less than 10% of all ICH.[15]

A growing source of secondary ICH, anticoagulant or fibrinolytic use accounts for approximately 10% of all ICH. Long term anticoagulant use increases the risk of ICH 10-fold.[15] Sudden severe elevation in blood pressure is another source of ICH seen commonly in malignant hypertension but rarely after carotid endarterectomy. Intracranial hemorrhage due to cocaine, amphetamine, or phenylpropanolamine use may be secondary to sudden elevation in blood pressure, multifocal cerebral vessel spasm, or drug-induced cellulites.[15] Secondary hemorrhages into brain areas after ischemic stroke or due to cerebral venous thrombosis can occur and reflect bleeding into compromised brain. Small areas of microhemorrhage can coalesce in a delayed fashion after severe head trauma. This occurs commonly at gray and white matter interfaces and usually reflects substantial pathologic damage.

Risk Factors.

A meta analysis on the risk factors for intracerebral hemorrhage in the general population by Ariesen et al.[16] identified 4 significant risk factors for ICH: hypertension, age, male sex and alcohol intake. Current smoking and diabetes mellitus are weak risk factors. Data are inconclusive for physical activity. Ever smoking was no risk factor. Data for hypercholesterolemia were conflicting. However, cumulative data on cholesterol suggested a lower risk of ICH with higher cholesterol level. In addition to the various factors mentioned above, genetic study of primary intracerebral hemorrhage have begun to yield important biologic insights into the pathogenesis of ICH.

(1)Hypertension.

The most notable and modifiable risk factor for ICH is the presence of hypertension.[17] Hypertension, detected in most patients with ICH, is the basis for the term hypertensive hemorrhage. Hypertension is the single most important modifiable risk factor for ICH. Approximately 75% of ICH patients have pre-existing hypertension.[18] Local study by Muiz et. al[19] reported that hypertension was seen in 60.7% of patients with ICH. The investigator of 11 case-control studies showed a positive association between hypertension and ICH.[16] The overall OR was 3.68 (95% CI, 2.52 to 5.38). Retrospective studies have shown that high blood pressure confers a two to six fold increase in the risk of ICH.[20] Patients with recognized hypertension who discontinued their anti-hypertensives have a twofold increase in the risk of ICH relative to those who remain compliant with medication. Risk of ICH in patients with preexisting hypertension appears to be related to the severity and duration of hypertension. The exact quantification of risk is difficult to ascertain, but a response curve similar to the pack-year concept with smoking probably exists.[4]

(2)Age and Sex.

The incidence of ICH increases exponentially with increasing age, with rates doubling every 10 years after age 35 years.[5] The overall mean age for patients with ICH is 61 years. There is a slight male predominance. The investigator of 5 cohort studies reported on age and risk of ICH with the crude RR was 1.06. The RR for men compared to women was 4.64 (95% CI, 4.02 to 5.40).[16]

(3)Alcohol.

Several case-control studies have implicated heavy alcohol intake as a risk factor for ICH.[21] This effect may be mediated partially by hypertension, although studies controlling for hypertension have supported an independent effect of alcohol. The reason for this may relate to impaired coagulation or platlet function or an increase in cardiac arrythmias leading to increased cardioembolic hemorrhagic infarctions.[22] Moderate alcohol use does not raise the risk, although there does appear to be a dose-related increase in the odds-ratio of ICH.[20] The investigator of 8 case-control studies reported on alcohol intake and association with ICH.[16] Because the definition of high alcohol intake differed in the studies from >36g/d to >100g/d , the authors arranged the studies according to cut off point from low to high. The overall OR was interpreted at an approximate mean cutoff of 56g/d, the weighted mean. The OR at this cutoff was 3.36 (95%CI, 2.21 to 5.12). These studies indicate a possible trend of higher risk of ICH with higher alcohol intake.

(4)Smoking and Diabetes Mellitus.

Metaanalysis by Arisien et al.[16] concluded that current smoking and diabetes mellitus are weak risk factors for ICH. Ever smoking was no risk factor. The overall OR for current smoking was 1.25 (95% CI, 0.94 to 1.66). The overall OR for diabetes mellitus was 1.27 (95% CI, 0.98 to 1.65).

(5)Serum cholesterol.

An association between low total serum cholesterol levels and ICH was initially observed in Japanese patients.[7] Other studies have shown low cholesterol to be associated with increased rate of ICH only in combination with other risk factors including age and hypertension.[23] The Multiple Risk Factor Intervention Trial[24] and a recent case control study[25] reported that cholesterol level lower than 160 mg/dl imparted a 3-fold increase risk of ICH in hypertensive middle-aged men. Nevertheless, the precise aetiological role of serum cholesterol in the pathogenesis of ICH is incompletely understood. Importantly, treatment of hypercholesterolemia does not appear to confer an increased risk of hemorrhage.[26]

(6) Genetic Risk factor for ICH.

A study by O'Donnell et al[27] reported that the presence of the epsilon 2 and epsilon 4 alleles of the apolipoprotein E (APOE) gene was associated with a tripling of the risk of recurrent hemorrhage among survivors of lobar intracerebral hemorrhage related to amyloid angiopathy. These alleles are associated with increased deposition of beta-amyloid protein and degenerative changes such as fibrinoid necrosis in the vessel wall. The expression of either allele appears to increase the risk of intracerebral hemorrhage by augmenting the vasculopathic effects of amyloid deposition in cerebral vessels. This two APOE alleles appear not only to increase the risk for cerebral amyloid angiopathy occurrence, but also to lower the age of first hemorrhage[27] and to shorten the time to recurrent ICH. In 70 consecutive survivors of an initial lobar ICH studied by O'Donnell et. al[27], carriers of APOE ε2 or ε4 rebled at 2-year rate of 28% compared with only 10% for patients with the common APOE ε3/ε3 genotype. A study by Woo et al[28] on genetic and environmental risk factors for

intracerebral hemorrhage showed that the presence of APOE ε2 and ε4 associated with an adjusted odds ratio for lobar ICH of 2.3 in the studied population, accounting for attributable risk of 29% of all lobar ICH. His study also found that half of all cases of non-lobar ICH are attributable to hypertension. The presence of APOE ε2 and ε4 in non-lobar ICH was statistically not significant. His study supported the hypothesis that the pathogenesis of lobar ICH may differ from nonlobar ICH.

PATHOPHYSIOLOGY.

Intracerebral hemorrhages commonly occur in the basal ganglia, cerebral lobes, thalamus, brain stem predominantly the pons and cerebellum. In a consecutive series of 109 cases of ICH, the most common site of bleeding were the basal ganglia (42%), lobar (40%), cerebellum (8%), brain stem (6%) and thalamus (4%).[29] Extension into the ventricles occurs in association with deep, large hematomas. Edematous parenchyma, often discolored by degradation products of hemoglobin, is visible adjacent to the clot.The anatomical location and computed tomographic images of the common sites of intracerebral hemorrhage is shown in Figure 2.1.

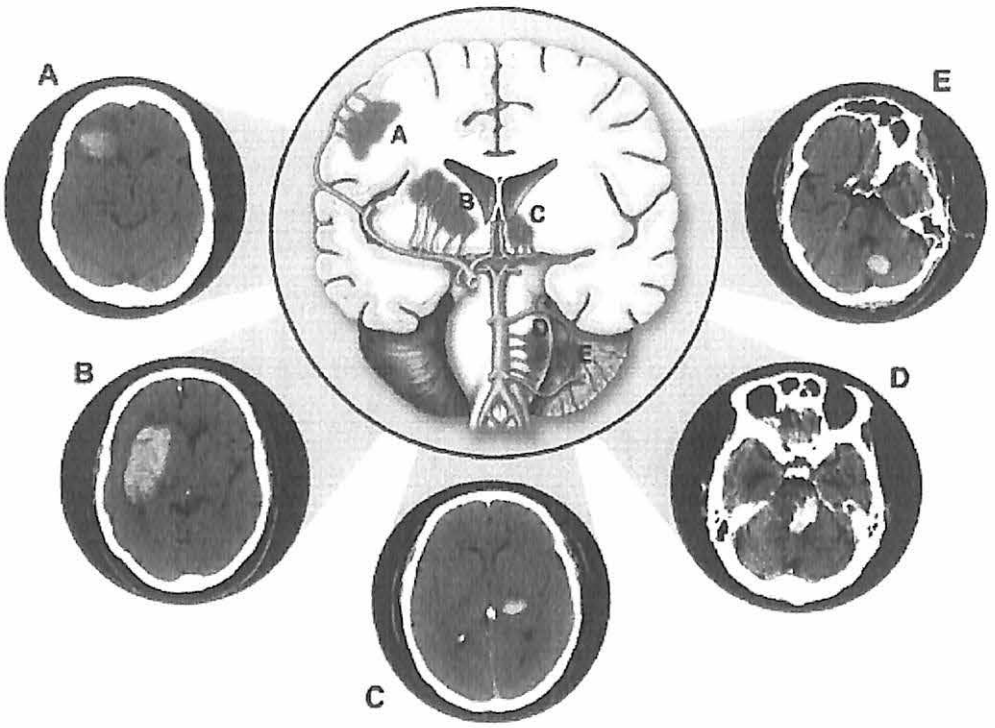

Figure 2.1: Anatomical location and computed tomographic images of the common sites of intracerebral hemorrhage.(A) Lobar or deep white matter, (B) Basal ganglia, (C) Thalamus, (D) Pons and (E) Cerebellum. (From Manno EM, Atkinson JLD, Fulgham JR, et al. Emerging medical and surgical management strategies in the evaluation and treatment of intracerebral hemorrhage. *Mayo Clin Proc.* 2005;80(3):420-433)

Histologic sections are characterized by the presence of edema, neuronal damage, macrophages, and neutrophils in the region surrounding the hematoma.[30] The hemorrhage spreads between planes of white matter cleavage with minimal destruction, leaving nests of intact neural tissue within and surrounding the hematoma. This pattern of spread accounts for the presence of viable and salvageable neural tissue in the immediate vicinity of the hematoma.

Hypertensive intracranial hemorrhage occurs in areas of the brain that are perfused by the perforating arteries that arise directly from the large basal cerebral arteries. These perforating arteries are directly exposed to the effect of hypertension because they lack the protection normally afforded by a preceding gradual decrease in vessel

calibre.[31] Chronic hypertension induces a series of pathologic changes that lead to segmental constriction of these vessels. This process was labeled lipohyalinosis by Fisher.[32]

Lipohyalinosis represents 2 pathologic processes that include atherosclerosis of the larger (100-500 mm) perforating arteries and arteriosclerosis of the smaller (<100 mm) perforating vessels. Atherosclerosis occurs most commonly at the branch point of vessels and is characterized by subintimal fibroblast proliferation accompanied by deposition of lipid-filled macrophages. Arteriosclerosis involves the replacement of smooth muscle cells in the tunica media with collagen. These processes result in the development of noncompliant, narrowed vessels that are susceptible to both sudden closure (lacunar infarction) or rupture that manifest as intracerebral hemorrhage. The mechanism of actual hemorrhage is presumably due to rupture of these fragile vessels, but this has been difficult to prove pathologically. Cerebral microaneurysms, described by Charcot and Bouchard[33] and further delianeted by Fisher[34] are described in only a small number of patients. Hemorrhagic expansion of fibrin or bleeding globules of tissue have been described but are believed to be limited to ICH secondary to sudden elevations in blood pressure.

Intracerebral hemorrhage due to cerebral amyloid angiopathy (CAA) resulted from the deposition of the insoluble beta amyloid protein in the tunica media and adventitia of leptomeningeal and cortical arteries, arterioles and capillaries.[35] Beta amyloid replaces the smooth muscles of the tunica media, making the artery less compliant. The presence of amyloid in blood vessels increases exponentially with age and is found in up to 58% of patients over the age of 90 years. CAA-related ICH in some cases may be related to an interaction with other risk factors, notably hypertension.[36] CAA-related hemorrhages are cortical or subcortically based, often large and have a

propensity for extension into the subarachnoid space and ventricles.[37] Recurrence of lobar ICH is also indicative of amyloid angiopathy.[38] It should be noted however that the diagnosis of CAA can only reliably be made by histopathology.[39]

The initial clinical effects of intracerebral hemorrhage are the result of direct destruction and displacement of surrounding brain tissue that occur during hemorrhage. The blood appears to dissect tissue planes, compressing adjacent structure. Initially, intracerebral hemorrhage was considered to be a monophasic event that stopped quickly as a result of clotting and tamponade by the surrounding regions. Subsequent neurologic deterioration was attributed to the development of cerebral edema. However, it is now accepted that a large percentage of patients will develop hemorrhagic expansion of their initial bleeding. Brott et al.[40] in a prospective observational study of patients evaluated within the first 3 hours after ictus, described ICH expansion in 26% of patients within the first hour after hospital admission. Another 12% of patients experienced ICH volume expansion within 20 hours after admission. Hematoma larger than 25 mls are more likely to grow in the first 6 hours from symptoms. Hematoma expansion after the first 24 hours is rare.[41] The ICH volume can increase by as much as 40% and is associated with neurologic deterioration. A study by Kazui et al.[42] suggested that poorly controlled diabetes mellitus and systolic blood pressure greater than 200 mmHg on hospital admission were associated with hematoma volume expansion.

The mechanisms of secondary tissue injury are less well defined. Rebleeding can occur, causing further tissue destruction and increased mass effect. Cerebral herniation can occur as a consequence of the hematoma mass effect. Hydrocephalus can develop and produce marked elevation in intracranial pressure, which may produce cerebral herniation. However, the neurological deterioration after initial

hemorrhage is often attributed to the development of cerebral edama.[43] An animal models of intracerebral hemorrhage have shown that blood is irritating to the parenchyma, and there is an area of edema, ischemia and hemorrhagic necrosis at the margin of the clot, so called the ischemic penumbra.[44] Experimental studies in animals have suggested that early removal of mass lesion can reduce the ischemic damage.[45]

The development of cerebral edema in ICH appears within hours secondary to clot retraction with extrusion of plasma protein into the underlying white matter.[43] Later, delayed thrombin formation may contribute directly to neural toxicity or indirectly through damage to the blood-brain barrier with subsequent worsening of vasogenic edema. Peak edema occurs 3 to 7 days after the hemorrhage and correlates with lysis of red blood cells. Both hemoglobin and its degradation products have been implicated in direct and indirect neural toxicity.[43] The importance of the development of cerebral edema in ICH has been supported by retrospective evidence suggesting that patients with a larger amount of cerebral edema relative to the initial hemorrhage volume have worse clinical outcome.[46]

The role of ischemia in the pathophysiology of ICH is unclear. Numerous cerebral blood flow (CBF) studies have described an area of decreased perfusion surrounding a cerebral hemorrhage,[47,48] suggesting that large areas of brain surrounding ICH may be at risk of ischemia. In 1988, Bullock et al.[49] studied the effect on regional cerebral blood flow in a primate model of intracerebral hemorrhage. The study showed a profound reduction in cerebral blood flow in the hemisphere ipsilateral to the induced hematoma, and most markedly in the clot penumbra. The lowest regional cerebral blood flow values were recorded in the immediate clot penumbra and were below threshold levels for ischemic neuronal damage for 90 minutes after the hemorrhage.

Likewise, cerebral blood flow measurements in human after spontaneous intracerebral hematoma using single-photon emission computed tomographic scanning have also revealed reduced flow levels, with the greatest reduction in the ipsilateral hemisphere, however these regional cerebral blood flow levels were well above the threshold levels known to cause ischemic damage.[47] Recent positron emission tomographic data have caused researchers to question the role of ischemia in ICH. Zazulia et al.[50] reported a normal oxygen extraction ratio in the perihematomal region, suggesting that this region is not ischemic and that the decreased perfusion occurs in response to decreased cerebral metabolism. A study by Peter et al.[51] assessing the presence of perihemorrhagic ischemic changes in a prospective stroke magnetic resonance imaging (MRI) study found no evidence for a perihemorrhagic and potentially salvageable ischemic penumbra in hyperacute ICH. However the subjects in this study is small, severely ill and comatose patients was not included and the ICH size is smaller than in general population.

CLINICAL PRESENTATION.

The clinical presentation of ICH depends on the size, location, and presence of intraventricular extension of the hemorrhage. Headache of variable intensity always occurs and may be accompanied by nausea and vomiting, focal signs, and progressive neurological deficits. The deficits may not follow a typical infarction distribution pattern in patients with large artery stroke. Seizures occur in approximately 10% of all patients with ICH and in almost one half of patients with lobar hemorrhage. Almost all seizures occur at the onset of bleeding or within the first 24 hours of ictus and are non predictive of the development of delayed epilepsy.[52]

Patients harbour large hemorrhages usually present in stupor or coma. This may be secondary to elevated intracranial pressure (ICP) leading to decreased cerebral perfusion or due to direct infiltration or distortion of diencephalic or brainstem structures.[53] Patients with blood extending into the ventricular system often experience a reduced level of alertness because of ventricular ependymal irritation or the development of hydrocephalus.

In one fourth of patients with intracerebral hemorrhage who are initially alert, deterioration in the level of consciousness occurs within the first 24 hours after onset of cerebral hemorrhage.[54] The presence of a large hematoma and ventricular blood increases the risk of subsequent deterioration and death. Expansion of the hematoma is the most common cause of underlying neurologic deterioration within the first three hours of the onset of hemorrhage. Worsening cerebral edema is also implicated in neurologic deterioration that occurs within 24-48 hours after the onset of hemorrhage.[55] Infrequently, late deterioration is associated with progression of edema during the second and third weeks after the onset.[56]

The classic presentation of ICH is sudden onset of a focal neurological deficit that progresses over minutes to hours with accompanying headache, nausea, vomiting, decreased consciousness, and elevated blood pressure. In the Harvard Stroke Registry, 51% to 63% of patients with ICH had a smooth progression of neurological symptoms whereas 34% to 38% of patients had maximal symptoms at onset. By comparison, only 5% to 20% of the various ischemic stroke subtypes and 14% to 18% of patients with SAH had gradual progression of symptoms.[57] As previously mentioned, the early progression of neurological deficit in many patients with ICH is frequently due to ongoing bleeding and enlargement of hematoma during the first few hours.[40]

Patients with ICH uncommonly present with symptoms on awakening from sleep (15%).[57] An early decrease in level of consciousness is seen in approximately 50% of patients with ICH, an uncommon early finding in patients with ischemic stroke. Vomiting is an important diagnostic sign, particularly if the hematoma lies within the cerebral hemisphere. The Harvard Stroke Registry reported that 49% of patients with supratentorial ICH vomited compared with 2% of patients with ischemia in the carotid territory and 45% of patients with SAH.[57] Elevation of blood pressure, often to very high levels, occurs in as many as 90% of patients with ICH.

DIAGNOSIS.

Despite the differences in clinical presentation between hemorrhagic and ischemic strokes, no collection of clinical features has sufficient predictive value to forego brain imaging. The diagnostic study of choice in ICH is noncontrasted Computed Tomography (CT). CT scan clearly differentiates hemorrhagic from ischemic stroke. It also demonstrates the location of the hemorrhage and may reveal structural abnormalities such as aneurysms, arteriovenous amlformations, and brain tumors that cause ICH as well as structural complications such as herniation, intraventricular hemorrhage, or hydrocephalus. Administration of contrast can often highlight suspected vascular abnormalities. The possible causes of hemorrhage can be determined by its location in the brain as seen on the CT scan, the presence of structural abnormalities as seen in brain imaging, associated medical conditions such as hypertension, and the patient's age. Hemorrhages that originate in the deep subcortical structures such as putamen, caudate, thalamus, pons, cerebellum, or periventricular deep white matter, particularly in patients with a history of hypertension result from rupture of the deep perforating arteries. Lobar intracerebral

hemorrhages in the very elderly are often thought to be due to amyloid angiopathy. However, this assumption may be incorrect, as in the majority of patients with lobar hemorrhage have a history of hypertension.[18]

Magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) have emerged as other useful tools for detecting structural abnormalities such as malformations and aneurysms.[58] Although MRI may miss small aneurysms and vascular malformations, it is superior to CT and angiography in detecting cavernous malformations. In addition, MRI is also useful for dating hemorrhages. MRI is limited in early detection of ICH by the time required to obtain imaging and by the limited ability to monitor a patient while in the scanner.[59]

The role of cerebral angiography in ICH has been addressed by 3 studies. Zhu et al[60] reported low yield from cerebral angiography in identifying an underlying lesion in patients older than 45 years who had history of hypertension and had hemorrhages in deep subcortical structures. However, Halpin et al[61] reported a different finding. He conducted a study to examine the role of angiography in ICH patients whose mean age was 49 years (range 10-70). CT findings that prompted the impression of a structural lesion were the presence of subarachnoid or intraventricular hemorrhage, abnormal intracranial calcification, prominent vascular structures, or the site of hemorrhage (eg, perisylvian hemorrhage). Of the 44 patients with these CT findings, 38 underwent angiography. The angiographic findings were positive in 32 of the 38 cases (84%) with identification of arteriovenous malformations in 23 patients and aneurysm in 9. Angiography was not performed for clinical reasons in 6 patients, and no abnormality was seen in the remaining 6. On the basis of CT findings, 58 patients were not thought to have an underlying structural lesion, but 42 underwent delayed angiography. Angiographic findings were positive in 10 patients in this group (24%),

revealing unsuspected arteriovenous malformation in 8 (19%) and aneurysm in 2 (5%). In a study by Ishak et. al,[62] 54 patients with an intracerebral hemorrhage who underwent both CT examination and six-vessel cerebral angiography were studied over a 2-year period. An angiography detected vascular lesion in 50% of cases, 38.9% aneurysm and 11.1% arteriovenous malformation (AVM). In the aneurysm group, angiographic yield was 34.3% and in the AVM group, it was 37.9%. His study suggested that cerebral angiography is justified in patients with pure subarachnoid hemorrhage (SAH). The diagnostic cerebral angiography is indicated for patients with ICH and SAH and IVH with a history of hypertension, regardless of age.

Other useful diagnostic tools include a complete blood count, prothrombin time, activated partial thromboplastin time, electrolytes, electrocardiography, and chest x-ray. The white cell count can detect underlying infection such as hemorrhages associated with endocarditis. Hemoglobin analysis may also provide clues to diagnosis and as an indicator of blood loss. Prothrombin time and activated partial thromboplastin time may offer clues to coagulation problems, either iatrogenic or acquired. Electrolytes can reveal evidence of primary renal failure as an associated cause of ICH or disturbances in sodium that may accompany brain hemorrhage. Electrocardiography can reveal underlying dysrhythmia or myocardial ischemia associated with brain hemorrhage. Chest x-ray may reveal underlying aspiration or another pulmonic process that may complicate treatment.

MANAGEMENT.

Due to lack of a proven medical or surgical treatment for ICH, there have been a great variation with regard to medical and surgical treatment for ICH.[63] Although guidelines based on scant data from randomized trials are uncertain at best and may be wrong at worst, they can provide a reasonable treatment approach at present.

Initial Management in the Emergency Department.

Initial management should first be directed towards the basic of airway, breathing, and circulation, and detection of focal neurological deficits. Examination should include looking for complications such as pressure sores, compartment syndromes, and rhabdomyolysis in patients with prolonged depressed level of consciousness. The patient's level of consciousness must be monitored closely because neurologic deterioration can occur quickly with hematoma expansion or with rupture into ventricular system.

Airway and Oxygenation.

Although intubation is not required for all patients, airway protection and adequate ventilation are critical. Patients who exhibit a decreasing level of consciousness or signs of brain stem dysfunction are candidates for aggressive airway management. Intubation should be guided by imminent respiratory insufficiency rather than an arbitrary cutoff such as a specific Glasgow Coma Score (GCS). Intubation is indicated for insufficient ventilation as indicated by hypoxia ($pO_2 < 60$ mmHg or $PCO_2 > 50$ mmHg) or obvious risk of aspiration with or without impairment of arterial oxygenation.

Endotracheal intubation must be performed in a controlled setting by an experienced physician. Pharmacological agents and intubation techniques should be used to ensure rapid and smooth airway control along with medications designed to block increases in ICP. Lidocaine (1.0 – 2.0mg/kg of body weight, or propofol, 10-20 mg in incremental doses) can be used for induction. Midazolam is generally avoided because of unfavorable effects on ICP during induction, although the clinical importance of this is uncertain. Neuromuscular paralysis ideally should be avoided and may be unnecessary in many instances. When required for airway control, a short-acting nondepolarizing agent such as atracurium besylate (0.3 -0.4 mg/kg of body weight IV) or vecuronium bromide (0.2 – 0.3 mg/kg of body weight IV) is preferred. Paralysis should be discontinued as quickly as possible to allow for monitoring of the neurologic examination.[59] Once the airway is secured, mechanical ventilation should be set to ensure adequate oxygenation and ventilation. If elevated ICP is suspected, an intermittent mandatory ventilation volume and rate should be set to attain a PCO2 of 30 to 35 mmHg. Endotracheal tubes with soft cuffs can generally be maintained for <2 weeks. In the presence of prolonged coma or pulmonary complications, elective tracheostomy should be performed after 2 weeks.

Medical Management.

To date, 4 small randomized trial of medical therapy for ICH have been conducted. Steroid versus placebo treatment,[64,65] hemodilution versus best medical therapy,[66] and glycerol versus placebo.[67] All these studies found no significant benefit for the 3 therapies. In addition, Poungvarin et al[64] reported that patients who were treated with steroids were more likely to develop infectious complications than those treated with placebo. Recently, Meyer et al[68] conducted a randomized study assessing the role of

recombinant activated Factor VII (rFVIIa) for acute intracerebral hemorrhage in 399 patients diagnosed by CT scan within 3 hours after the onset of ICH. This study found that treatment with rFVIIa within four hours after the onset of hemorrhage limits the growth of the hematoma, reduces mortality and improved functional outcome at 90 days, despite a small increase in the frequency of thromboembolic adverse events.

Blood Pressure Management.

The management of blood pressure in ICH is somewhat controversial. At present, the only guidelines for blood pressure management in ICH are provided by the AHA Stroke Council, which suggests acutely lowering mean arterial pressures > 130mmHg.[3] The optimal level of a patient's blood pressure should be based on individual factors such as chronic hypertension, elevated intracranial pressure (ICP), age, presumed cause of hemorrhage, and interval since onset.

The theoretical rationale for lowering blood pressure is to decrease the risk of ongoing bleeding from ruptured small arteries or arterioles. However, a prospective observational study by Brott et al[40] assessing the growth in the volume of ICH did not demonstrate a relation between the baseline blood pressure and subsequent growth of ICH, but frequent use of hypertensive agents in this study may have obscured any relationship. Conversely, overaggressive treatment of blood pressure may decrease cerebral perfusion pressure and theoretically worsen brain injury, particularly in the setting of increased intracranial pressure. In a study by Abdullah J and colleagues[69] assessing the effect of management of reduction of hypertensive encephalopathy associated with intracerebral hemorrhage, they found that patients with systolic blood pressure between 140 to 160 mm Hg tolerated a mean blood pressure (MAP) of 60 and lower and in patients with a higher systolic blood pressure of 160-180 mm Hg,

they did not tolerate the MAP of 60 or less and required a MAP of 80 to 100 mm Hg to maintain a cerebral blood flow (CBF) > 80ml/100g/min and a transcranial Doppler flow (TCD) of 50-100 cm/sec.

The AHA Stroke Council recommends that blood pressure levels be maintained below a mean arterial pressure of 130 mmHg in person with a history of hypertension. These guidelines are based on non-randomised retrospective and anecdotal trials. In patients with elevated ICP who have an ICP monitor, cerebral perfusion pressure should be kept >70 mmHg. Mean arterial blood pressure >110 mm Hg should be avoided in the immediate postoperative period. If systolic arterial blood pressure falls below 90 mmHg, pressors should be given. The suggested management is summarized in Table 2.2.

Blood Pressure Management in ICH.
1.Elevated blood pressure (suggested medications) Labetolol 5-100 mg/h by intermittent bolus doses of 10-40 mg or continuous drip (2-8 mg/min). Esmolol 500 μg/kg as a load; maintenance use, 50-200 μg/kg/min. Nitroprusside 0.5-10 μg/kg/min. Hydralazine 10-20 mg 4-6 hourly. 1. If systolic BP is >230 mmHg or diastolic BP > 140mmHg on 2 readings 5 minutes apart, institute nitroprusside. 2. If systolic BP is 180 to 230 mmHg, diastolic BP 105-140 mmHg, or mean arterial pressure > 130 mmHg on 2 readings 20 minutes apart, institute intravenous labetolol, esmolol or other small doses of easily titratable intravenous medications such diltiazem or verapramil. 3. If systolic BP is < 180 mmHg and diastolic BP is < 105 mmHg, defer antihypertensive therapy. 4. If ICP monitoring is available, cerebral perfusion pressure should be kept at >70 mmHg.
2. Low blood pressure. Volume replenishment is the first line of approach. Isotonic saline or colloids can be used and monitored with central venous pressure pr pulmonary artery wedge pressure. If hypotension persists after correction of volume deficit, continuous infusion of pressors should be considered, particularly for low systolic blood pressure such as <90 mmHg.

Table 2.2: Guideline by the special writing group of the Stroke Council, American Heart Association (AHA)[3] on blood pressure management in ICH.