THE USE OF EARLY, MILD HYPOTHERMIA IN THE TREATMENT OF STABLE, SPONTANEOUS, SUPRATENTORIAL, INTRACEREBRAL HAEMORRHAGE

By

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MB.BCh.BAO, MRCSI

Dissertation submitted in partial fulfillment of the requirements for the Masters in Surgery (Neurosurgery)

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DEDICATION

For my dearest wife,

Rosfaiizah

And

My children,

Muhammad Harith
Adreanna Nurul Hidayah
Adreanna Nurul Husna

ACKNOWLEDGEMENT

My humblest appreciation to

- My late father, Hj. Husin b. Hj Jamil
- My mother, Hjh Saunah bt Hj Saijan
- My sister, Ainawati
- My teachers, Prof Jafri Malin Abdullah, Prof John Tharakan, Associate Prof. Hillol Kanti Pal, for guiding me through the program
- My friends and colleagues, for sharing with me their knowledge and experience
- The nameless people who had supported me in preparing this dissertation , I am forever indebted

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LIST OF ABBREVIATIONS

AHA	American Heart Association
ARDS	Acute Respiratory Distress Syndrome
BAEP	Brainstem Auditory Evoked Potential
BP	Blood Pressure
C	Celsius
CBF	Cerebral Blood Flow
CNS	Central Nervous System
CPP	Cerebral Perfusion Pressure
CI	Confidence Interval
CT	Computerised Tomography
CMRO2	Cerebral Metabolic Rate Oxygen
DM	Diabetes Mellitus
EDH	Extradural Haematoma
EP	Evoked Potential/Response
GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Score
HR	Heart Rate
ICP	Intra Cranial Pressure
INR	International Normalised Ratio
IVH	Intra Ventricular Haemorrhage
MRI	Magnetic Resonance Imaging
NIHSS	National Institute of Health Stroke Scale

mRS	Modified Rankin Scale
PET	Positron Emission Tomography
rTPA	recombinant Tissue Plasminogen Activator
USM	Universiti Sains Malaysia
VEP	Visual Evoked Potential
WHO	World Health Organisation

PENGGUNAAN PENYEJUKAN RENDAH DAN AWAL DALAMAN DALAM PROSES PERAWATAN PENDARAHAN DALAM OTAK YANG STABIL.

ABSTRAK

Pendarahan dalam otak adalah satu kondisi yang masih membawa kesan yang teruk dengan pilihan rawatan yang amat terhad. Pengunaan penyejukan dalam proses perawatan angin ahmar (ischaemic stroke) telah dibuktikan dengan kesan yang memberangsangkan namum masih belum dipastikan. Objektif kajian ini adalah untuk melihat kesan penggunaan penyejukan rendah awal dalam proses perawatan pesakit pendarahan dalam otak yang stabil dengan menggunakan skala strok pada 7 hari, 30 hari dan 90 hari. Satu kajian prospektif tanpa rambang dijalankan di Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan dengan menggunakan pesakit dengan pendarahan dalam otak berumur di antara 18 hingga 80 tahun. Pesakit-pesakit dengan pendarahan dalam otak yang telah dipastikan menggunakan imbasan CT, tidak menjalani sebarang jenis pembedahan (termasuk penebukan ventrikel) di cadangkan untuk memasuki kajian ini. Pesakit yang bersetuju dan memberikan kebenaran bertulis telah disejukkan dengan sistem penyejukan dalaman selama 24 jam , dan kemudian pemanasan semula secara perlahan-lahan, semuanya di lakukan dalam unit rawatan rapi. Pesakit-pesakit yang tidak memberikan kebenaran pula akan mengikuti perawatan piawai untuk pendarahan dalam kepala, dan pesakit-pesakit diambil sebagai kawalan. Kesemua pesakit-pesakit ini kemudiannya akan dipantau menggunakan skala antarabangsa National Institute of Health Stroke Scale (NIHSS) dan modified Rankin Scale (mRS) pada rawatan susulan 7 hari, 30 hari dan 90 hari. Sejumlah 24 orang pesakit telah terpilih untuk mengikuti kajian

ini. 6 orang pesakit telah menjalani penyejukan dalam namun 2 orang pesakit telah meninggal dunia sebelum 7 hari , sementara 18 orang dipilih sebagai kawalan dan 3 orang meninggal dunia sebelum 90 hari.. Terdapat kesan yang bermakna secara statistik pada skala mRS untuk rawatan susulan pada 30 hari dan 90 hari. Dengan menggunakan skala NIHSS, terdapat kesan baik yang bermakna pada penggunaan penyejukan pada 7 hari, 30 hari dan 90 hari. Kami hanya boleh menyimpulkan bahawa penyejukan rendah dan awal adalah berkesan dan boleh digunakan sebagai rawatan tambahan untuk pendarahan dalam otak. Namun dengan batasan kajian ini, kami mencadangkan satu kajian yang lebih besar, dengan menggunakan beberapa pusat kajian, untuk melihat kesan penyejukan rendah pada pesakit dengan pendarahan dalam kepala secara lebih pasti.

THE USE OF EARLY, MILD HYPOTHERMIA IN THE TREATMENT OF STABLE, SPONTANEOUS, SUPRATENTORIAL, INTRACEREBRAL HAEMORRHAGE.

ABSTRACT

Haemorrhagic stroke or spontaneous intracerebral haemorrhage is a devastating condition that usually carries a poor prognosis and the treatment options has been very limited. The use of therapeutic hypothermia in ischaemic stroke has been published with some encouraging results but not definite. The objective of the study is to see the effect of mild hypothermia in the early post haemorrhagic stroke patient with a stable condition assessed using standard stroke outcome score in seven days, 30 days and 90 days. A prospective non randomised study was done with the sample of confirmed haemorrhagic stroke patients presenting to Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan between the ages of 18 to 80 years. Patients with haemorrhagic stroke that was confirmed on CT scan, and did not undergo any surgical intervention (including ventriculostomy) were offered to be recruited into the study. The patients who consented underwent therapeutic hypothermia using an intravascular cooling catheter for 24 hours and then a period of slow rewarming, all these in an intensive care setting. Patients who did not consent to the procedure were treated as per standard haemorrhagic stroke treatment protocol and taken as control. All patients would then be assessed in seven days, 30 days and 90 days using the National Institute of Health Stroke Scale (NIHSS) and Modified Rankin Scale. A total of 24 patients were recruited. In the interventional

arm, six patients were recruited. Two of the patients however died in the first week of the therapy. In the control arm, 18 patients were recruited and 3 died before the 90 days follow up. There was a statistically significant improvement of the mRS score of the hypothermia group compared to the control group at 30 days and 90 days follow up. Using the NIHSS score, the seven days, 30 days and 90 days follow up showed a little improvement in the hypothermia group compared to the control group, but statistically significant. It can be concluded that the use of mild hypothermia is feasible and may be adjunctive to other treatment in the management of haemorrhagic stroke. However, due to the study limitation, we recommend a larger, multicentred trial to be done on early mild hypothermia on haemorrhagic stroke.

1. INTRODUCTION

The quest for treatment of medical conditions has been the goal of doctors from ancient times. The ultimate goal is to find a cure, and if that is not possible, to alleviate the symptoms of the disease. Haemorrhagic stroke has been and will be a condition that doctors will face more frequent in the future. The treatments of this condition are mainly supportive and prevention may still be the best treatment.

Therapeutic hypothermia has been used since ancient times to treat medical ailments. Even without detailed knowledge of the scientific background of it physiological effect, man has harnessed the positive effect of cooling in the treatment of many diseases. In the last 2 decades, interest has grown in the field of hypothermia in the treatment of stroke. We have, now, better knowledge of the physiological effect and maybe the pharmacological effect of hypothermia, on the human body and its diseases.

2. STROKE

Stroke is defined by WHO criteria as rapidly developed clinical signs of focal disturbance of cerebral function, lasting >24 hours or leading to death, with no apparent cause other than vascular origin. From this working definition, stroke can be ischaemic (due to blockage) or haemorrhagic (due to vessel rupture). Stroke is the second most common cause of death in the world((WHO), 1997) and the leading cause of disability in people over the age of 65 years (Kaste *et al.*, 1998).

2.1. Prevalence of ICH

Intracerebral haemorrhage or also known as haemorrhagic stroke is an acute and spontaneous extravasation of blood into the brain parenchyma (Mayer and Rincon, 2005). It has been one of a few conditions where the prognosis of the patient has remained poor despite the medical advances in the field of medicine (Sacco and Mayer, 1994). Intracerebral haemorrhage (ICH) accounts for about 10-30% of all stroke with worse disability, morbidity and 6 months mortality of 30-50% (Sacco and Mayer, 1994).

2.2. Epidemiology of ICH

Current data suggest that annually in the USA, ICH has a frequency of about 37,000-52,000 (Broderick *et al.*, 1999, Taylor *et al.*, 1996). The overall incidence in one population based study was found to be 12-15 cases per 100,000 people per year (Gebel and Broderick, 2000).

In Malaysia, there is no current official data on the incidence of haemorrhagic stroke. . Limited data from our institution published in 2002 showed 158 cases of stroke admitted between 1997 and 1998 but this could not be extrapolated to the whole country (Jaya *et al.*, 2002) . The frequently quoted number for annual frequency of stroke in total is about 40,000, but this is only based on limited epidemiological data and is hospital based. Based on our own institution's experience, we felt that it would correspond to the international published rates and it is increasing. The burden of the disease on the society and government is increasing as lifestyle and diet in Malaysia has changed to mimic other parts of the western world. As well as that, with the improved healthcare infrastructure many more patients with haemorrhagic stroke will be admitted and treated in hospitals, thus increasing the number of patients surviving with severe disability.

2.3. Diagnosis of ICH

ICH is diagnosed by radiographic imaging such as CT scan or MRI scan.

2.3.1. CT scan

ICH diagnosis is confirmed on CT scan in most cases. This will be the gold standard. Careful and details inspection of the pattern and topography of the ICH can sometimes give clues about secondary causes of ICH such as associated subarachnoid haemorrhage (suggestive of aneurysm), multiple inferior and temporal haemorrhage (suggestive of trauma) and fluid level within the haematoma (suggestive of coagulopathy or anaemia) (Mayer and Rincon, 2005).

2.3.2. Volume of ICH

Rapid estimation of the volume can be made based on the CT scan by using the ABC/2 method, whereby A, B and C are the largest diameters of the clot seen on the CT scan. (Kothari *et al.*, 1996).

2.3.3. Sites of ICH

The typical sites for the ICH due to hypertension are (Qureshi *et al.*, 2001):

1. Basal ganglia (putamen, thalamus, caudate nucleus)
2. Pons
3. Cerebellum
4. Deep hemispheric white matter
5. Brain stem

Some authors had published the actual frequencies of the above sites but the list above had been given in descending order of frequencies, with almost 50% of the ICH secondary to hypertension occurring in the basal ganglia.

2.3.4. MRI

MRI is as sensitive as CT for detection of ICH in the acute stage (Kidwell *et al.*, 2004) but more commonly used as a follow up study to rule out secondary causes such as arteriovenous malformation (presence of flow voids), amyloid angiopathy (chronic lobar microbleeds) or a tumour. The relative high cost and lesser

availability of MRI in many hospitals would also limit the use of MRI as a primary diagnostic method for ICH.

2.3.5. Angiography

Cerebral angiography is the diagnostic standard for vascular causes of secondary ICH, such as arteriovenous malformation, dural arteriovenous fistula, cortical vein thrombosis or vasculitis (Mayer and Rincon, 2005). In one study, no vascular malformations were found in people over the age of 45 years with a history of hypertension and an ICH in a classic hypertensive location (basal ganglia, cerebellum and pons) (Zhu *et al.*, 1997). Angiography should also be considered in young, non hypertensive patients with ICH with no obvious explanation for the haemorrhage.

2.4. Risk factors for spontaneous ICH.

2.4.1. Hypertension

Hypertension is the most important risk factors for ICH, accounting for about 60-70% (Brott *et al.*, 1986). Chronic hypertension causes degeneration, fragmentation and fibrinoid necrosis of small penetrating arteries in the brain, which can eventually result in spontaneous rupture (Fischer, 1971). Some patients have discrete arteriolar microaneurysms (Charcot-Bouchard Aneurysms) which are degenerative changes in the distal medium and small arterioles (Woo and Broderick, 2002).

2.4.2. Cerebral amyloid angiopathy (CAA)

This is the second most common cause and accounts for about 15% of cases (Qureshi *et al.*, 2001). In this disorder, there is deposition of ß-amyloid peptide in the small to medium sized blood vessels of the brain and leptomeninges, resulting in vascular fragility. This deposition increased the risk of lobar haemorrhage in the elderly. CAA is present in 50% of those above the age of 70 years (Vinters and Gilbert, 1981).These ICH are usually less severe than hypertensive ICH but can recur in about 5-15% of patients (Greenberg *et al.*, 2004). When blood pressure is controlled, risk of recurrent haemorrhage in patients with CAA can be reduced to as low as 2% (Arakawa *et al.*, 1998).

2.4.3. Heavy alcohol consumption (Gill *et al.*, 1991), hypocholesterolaemia (Segal *et al.*, 1999), cigarette smoking and use of antiplatelet (Saloheimo *et al.*, 2001) had been shown to be independent risk factors for ICH.

2.5. Secondary causes of ICH

These are the factors that may cause ICH and are considered secondary. This is due to the fact that their indirect effect on the brain tissue, either by vasculature or by the imbalance of biochemical factors (Mayer and Rincon, 2005). The factors are trauma, arteriovenous malformation, intracranial aneurysm, coagulopathy, haemorrhagic conversion of cerebral infarct, dural sinus thrombosis, intracranial neoplasm, cavernous angioma, dural arteriovenous fistula, venous angioma, CNS vasculitis and cocaine or other sympathomimetic drug exposure (Mayer and Rincon, 2005).

2.6. Clinical findings

Stroke is a clinical syndrome of focal neurological deficit lasting more than 24 hours due to vascular cause, as per WHO criteria stated above. However in the case of ICH as a subset of stroke, there can be additional symptoms that may present. Rapid onset of focal neurological deficit with clinical sign of high intracranial pressure (ICP) such as loss of consciousness, headache and vomiting suggest a diagnosis of ICH (Mohr *et al.*, 1978) . In ischaemic stroke, the above symptoms can be present but usually only when there is a large area of infarct which causes massive oedema and mass effect. Rapid deterioration to coma with motor posturing, suggest massive ICH, bleeding into the brainstem or acute hydrocephalus secondary to intraventricular haemorrhage. Over 90% of ICH patient will have hypertension exceeding 160/100 mmHg, whether or not they have history of preceding hypertension (Mohr *et al.*, 1978).

2.7. Pathophysiology of ICH

2.7.1. Early haematoma growth

Early haematoma growth is associated with neurological deterioration and poor clinical outcome (Gebel *et al.*, 2002). In a prospective study, Brott and colleagues has shown that in their study, 2/3 of their patients with ICH has evidence of growth within 1 hour of the baseline scan (Brott *et al.*, 1997). This indicated that some active bleeding processes had occurred. The most consistent risk factor for early haematoma growth is the time from symptom onset to baseline CT. The shorter intervals associated with a higher risk of enlargement

on subsequent scan. The location of ICH does not seem to have an effect on the risk of haematoma growth (Mayer and Rincon, 2005).

2.7.2. Perihaematoma brain injury

Brain tissue injury and swelling, which result in increased ICP or herniation related to compartmentalised mass effect, is the primary cause of neurological deterioration after the first day (Mayer *et al.*, 1994). Although, many of us think that swelling and oedema 'peak' at day 3 after onset, studies indicate that the number of patients of neurological deterioration is the highest on the first day of haemorrhage and falls progressively thereafter (Mayer *et al.*, 1994). Radiological evidence on CT will show increase in the extent of oedema and midline shift for up to 2 weeks, but no clinical correlation is found (Zazulia *et al.*, 1999).

It has been proposed about the possible creation of an ischaemic penumbra in the brain tissue immediately adjacent to an ICH (Siddique *et al.*, 2002), however PET and MRI studies done as early as 6 h after symptoms have not shown tissue ischaemia in perihaematoma regions (Schellinger *et al.*, 2003). Haematoma induce inflammatory response was identified in animal (Power *et al.*, 2003) and human studies (Castillo *et al.*, 2002).

2.8. ICH score

In 2001, Hemphill et al. has proposed a simple scoring system to prognosticate patients with ICH in terms of their 30 days survival (Hemphill *et al.*, 2001). It has the advantage of being simple in terms of use, and has been adopted by many authors. See Figure 6.

2.9. Prognosis

Mortality of ICH is almost 50% at 1 year (Vermeer *et al.*, 2002). Half of all deaths happen in the first 2 days after symptom onset (Broderick *et al.*, 1993), whereas most deaths take place after the first month are the result of secondary medical complications. Independent predictors of death at 30 days and at 1 year include ICH volume, coma, older age, intraventricular haemorrhage and Infratentorial location.(Broderick *et al.*, 1993, Hemphill *et al.*, 2001, Vermeer *et al.*, 2002). As discussed previously, the ICH score proposed by Hemphill et al. can be used to predict the 30 days mortality on admission.

2.10. Management of ICH

2.10.1. Emergency management

i. Airway

Reduced conscious level will cause loss of normal reflexes that maintain an open airway, thus necessitating endotracheal intubation and mechanical ventilation (Gujjar *et al.*, 1998). Failure to detect this airway loss can result in aspiration, hypoxaemia or hypercapnia which results in cerebral vasodilatation

and high ICP. Ventilation should be set to maintain a pCO2 of about 35mm Hg. Hypercapnia below 28mm Hg should be avoided because of the possibility of excessive vasoconstriction and exacerbation of ischaemia.

ii. Blood pressure

Increased blood pressure after ICH has been associated with high risk of deterioration and death (Willmot *et al.*, 2004, Terayama *et al.*, 1997, Fogelhorn *et al.*, 1997). Extreme hypertension should be managed aggressively in the first 6 hours to avoid reduction in CPP thus precipitating ischaemia in the perihaematoma region. American Stroke Association(ASA) guideline recommends mean arterial blood pressure be ≤ 130mm Hg for patients with ICH and history of hypertension (Broderick *et al.*, 1999). In all cases, systolic blood pressure (SBP) should be maintained above 90 mm Hg. It should be noted that 'normal' blood pressure is not the target of the therapy, but rather a high 'normal' values to maintain the cerebral 'set point' of these hypertensive patients.

Hypertension can be controlled acutely with repeated intravenous boluses of labetolol every 10 min in the emergency setting. In intensive care setting, the best control is via continuous infusion of labetolol, esmolol or nicardipine, as advised by ASA (Broderick *et al.*, 1999). Sodium nitroprusside should be avoided due to the tendency to cause cerebral vasodilation and high ICP (Cottrell *et al.*, 1978).

There is controversy regarding the initial treatment of blood pressure in patients, as discussed above. The National Institute of Health in 2005 gave its highest priority to a trial aggressive blood pressure control (mean arterial pressure, MAP of 110-120 mmHg) within the first 3 h of ICH onset.

2.10.2. ICP control

Emergency measures for ICP control are appropriate for stuporous or comatose patients or those who present with acute clinical signs of brainstem herniation. The head should be elevated to 30 °, 1- 1.5g/kg of 20% mannitol should be given by rapid infusion (Cruz *et al.*, 2002) and the patient hyperventilated to a pCO2 of 28-32 mmHg. These are measure to 'buy time' before a definite neurosurgical procedure such as craniotomy, ventriculostomy and ICP monitoring.

2.10.3. Haemostatic therapy

Eptacog alfa (recombinant activated factor VII (rFVIIa) Novoseven®, Novo Nordisk, AS) is a powerful initiator of haemostasis currently approved for the treatment of bleeding in patient with haemophilia who is resistant to factor VIII replacement therapy. There are suggestive evidence that rFVIIa may improve haemostasis in patient with normal coagulation profile (Aitken, 2004). One randomised, double-blind, placebo controlled study showed a limit of growth of haematoma by 50%, with associated with a reduction of 38% in mortality (Mayer *et al.*, 2005).

2.10.4. Reversal of anticoagulation

Warfarin anticoagulation increases the risk of ICH five to ten times (Wintsen *et al.*, 1984) and 15% of ICH cases are associated with warfarin use. Among patients with ICH, warfarin doubles the risk of mortality and increases the risk of progressive bleeding and clinical deterioration (Hart *et al.*, 1995). Patients with ICH receiving warfarin should be reversed immediately with fresh frozen plasma or vitamin K. Some authors even suggest treatment should not be delayed in order to check coagulation test (Mayer and Rincon, 2005) with the view that correction of the INR will take several hours in most patients.

There was a report describing the use of rFVIIa to speed the reversal of warfarin anticoagulation in patients with ICH (Sorensen *et al.*, 2003). A single intravenous dose of rFVIIa can normalise the INR within minutes, larger doses producing longer duration of effect (Erhardtsen *et al.*, 1998). Patients with ICH who have had anticoagulation therapy with unfractionated or low-molecular-weight heparin should be reversed with protamine sulphate (Wakefield and Stanley, 1996). Patients with thrombocytopaenia or platelet dysfunction can be treated with a single dose of desmopression (DDAVP), platelet transfusions or both (Mannucci *et al.*, 1983).