BOLUS ADMINISTRATION OF TRANEXAMIC ACID WITH A MAINTENANCE DOSE VIA INFUSION AND STRICT BLOOD PRESSURE CONTROL FOR NON-TRAUMATIC INTRACEREBRAL HEMORRHAGES

By

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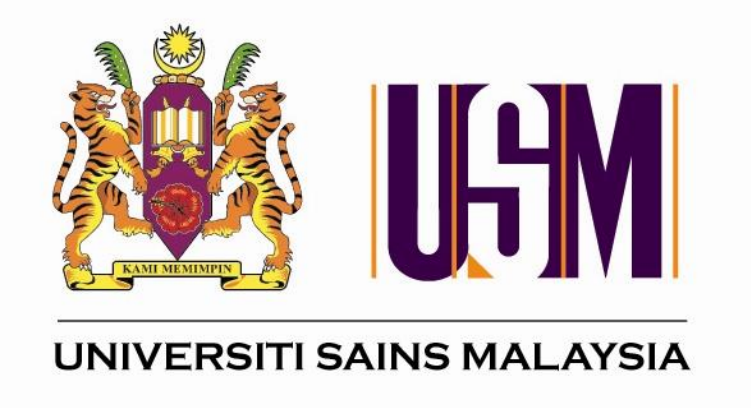

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ABSTRAK

TAJUK:

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PENGENALAN

Pendarahan spontan dalam otak merangkumi 10-15% daripada kes strok dengan insidens 10-30 kes per 100 000 orang setiap tahun dan dijangka akan meningkat 2 kali ganda dalam tempoh 30 tahun akan datang. Mortaliti dan morbiditi yang terkait dengan perdarahan spontan dalam otak masih tinggi. Sehingga kini masih tiada rawatan yang terbukti efektif untuk pendarahan spontan dalam otak. Faktor penting untuk meramal prognosis pesakit adalah pertambahan saiz hematoma. Tranexamic Acid (TXA) adalah ubat anti- fibrinolisis yang berkesan dalam mengurangkan pendarahan. Kajian ini adalah untuk menilai keberkesanan tranexamic asid berbanding placebo dalam menghalang pertambahan saiz pendarahan pada pesakit dengan pendarahan dalam otak

METODOLOGI

Dalam penyelidikan, a single blinded, randomized placebo-controlled trial. Labetolol digunakan untuk mencapai target sistolik tekanan darah 140-160 mmHg. Imbasan Otak (CT Brain)

dilakukan dalam tempoh 24 jam untuk menilai perubahan saiz hematoma. Objektif utama kajian ini adalah untuk menguji kesan tranexamic acid terhadap perubahan saiz pendarahan. Objektif lain yang ingin dicapai dengan kajian ini adalah menguji pelaksanaan dan kesan sampingan TXA ini terhadap pendarahan spontan dalam otak.

KEPUTUSAN

Seramai 30 orang pesakit direkrut dalam tempoh dari September 2012 dan Oktober 2013. Mean umur 45 tahun, dengan predominan lelaki (70%), paras tekanan darah sistolik 150 mmHg, mean skor kesedaran (GCS 13/15), median masa dari serangan stroke kepada perawakan (5.5 jam), masa dari perawakan kepada rawatan (20 minit) lokasi hematoma (internal capsule 80%, thalamus 13.3% dan head of caudate 6.66%). Mean pertambahan saiz hematoma adalah 0.16 ml dan 3.07mls masing- masing pada kumpulan yang diberikan TXA dan placebo. Analisis statistik menunjukan penurunan dalam peningkatan saiz hematoma dalam kumpulan TXA berbanding kumpulan placebo ($p<0.5$)

KESIMPULAN

Pesakit yang hadir dengan pendarahan dalam otak secara spontan akibat dari tekanan darah yang tidak terkawal yang mana tidak memerlukan pembedahan harus diberikan kombinasi rawatan dengan pemberian bolus ubat tranexamic acid 1 gram diiringi dengan dos infusi 1g / 8jam serta mengawal secara ketat bacaan tekanan darah dibandingan dengan pengawalan tekanan darah sahaja. Namun, kajian perawakan berganda harus dilakukan dengan melibatan pelbagai pusat rawat untuk tujuan evaluasi yang lebih signifikan.

ABSTRACT

Title

THE BOLUS ADMINISTRATION OF TRANEXAMIC ACID WITH A MAINTENANCE DOSE VIA INFUSION AND STRICT BLOOD PRESSURE CONTROL FOR NON-TRAUMATIC INTRACEREBRAL HEMORRHAGES

Introduction

Spontaneous intracerebral hemorrhages (ICH) account for 10–15% of all strokes with an incidence of 10–30 cases per 100,000 people/year, and their incidences are expected to double in the next 30 years. Mortality and morbidity associated with ICHs is still high. Until recently, there were no effective evidence-based treatments for acute ICH. ICH growth remains an important predictor of patient outcomes. Tranexamic acid (TXA), an anti-fibrinolytic drug, is known to reduce hemorrhaging in other conditions. The purpose of this study was to assess the effect of TXA compared to a placebo on the growth of hematomas in patients with spontaneous ICH.

Methodology

A single-blinded randomized placebo-controlled trial was conducted using TXA (intravenous 1 g bolus followed by an infusion of TXA at 1g/h for 8 h) in acute (<8 h) cases of primary ICH. Strict blood pressure control (target systolic blood pressure [SBP], 140–160 mmHg) was achieved using labetalol infusion. A repeat brain computed tomography (CT) was performed in the next 24 h to reassess the hematoma growth. The primary objective was to test the effect of TXA on hematoma growth. The secondary objective was to test the feasibility, tolerability, and adverse events of TXA in cases of primary ICH.

Results

Thirty patients were recruited between September 2012 and October 2013. The patients' mean age was 49 with male predominance (70%). The baseline SBP was 150 mmHg), mean Glasgow Coma Scale score was 13–15/15), and median time from stroke to the 1st CT scan was 5.5 h. The hematoma locations were as follows: internal capsule, 80%; thalamus, 13.3%; and head of caudate, 6.66%. The mean total hemorrhage growth was 0.16 mL and 3.07 mL in the treatment and placebo groups, respectively. Statistical analysis showed a reduction in the total hemorrhage growth in the TXA group in comparison to the control ($p < 0.05$).

Conclusions

Patients who present with spontaneous ICH secondary to uncontrolled hypertension should be treated with a combination of a bolus administration of TXA (1 g) and a maintenance dose via infusion (1 g/8 h) with strict blood pressure control, rather than blood pressure control alone. However, a double-blinded randomized study with multicenter involvement is needed for further evaluation of the significance of this finding.

1.0 INTRODUCTION

1.1 Incidence

Spontaneous, non-traumatic intracerebral hemorrhages (ICH) are a significant cause of morbidity and mortality worldwide. Despite substantial advances in neurovascular critical care, ICH remains the deadliest form of stroke and a major cause of neurological disability. Studies indicate that the proportion of ICH is higher in Asians than in Caucasians, with approximately 20–30% of ICH cases being hemorrhagic (van Asch et al. 2010).

Expansion of the initial hematoma strongly influences morbidity and mortality. The hazard ratio of mortality increases by 5%, with every 10% increase in ICH volume. In addition, each absolute increase in volume (mL) causes patient outcomes to be 7% more likely to shift from independence to dependence, as measured by the six-point modified Rankin Scale. Numerous other studies confirm the relationship of the hematoma expansion with neurological deterioration, poor functional outcome, and death. These relationships appear to be independent from the definition used for hematoma expansion. Moreover, data from the INTERACT 1 trial suggest a clear dose-response relationship between the magnitude of hematoma expansion and functional outcome and mortality, when using either the absolute or proportional definitions of expansion.

Outcome

To date, no individual treatment for ICH has shown a benefit in a randomized controlled trial, although specialized treatment provided at a neuroscience intensive-care unit (ICU) did appear to reduce mortality. Because of its strong relationship with outcomes and the potential to alter its course, hematoma expansion is an appealing therapeutic target. Candidate treatments aimed at

improving ICH outcomes potentially reduce hematoma expansion. However, mortality and morbidity rates associated with ICHs are still high. Until recently, there have been no effective evidence-based treatments for acute ICH. Thus, ICH growth remains an important predictor of patient outcome.

2 LITERATURE REVIEW

2.1 Spontaneous intracerebral hemorrhage

ICHs are an important public health problem associated with high rates of death and disability in adults. Although the number of hospital admissions for ICH has increased worldwide in the past 10 years, mortality rate has not decreased. The results of clinical trials and observational studies suggest that coordinated primary and specialty care is associated with a lower mortality than typical community practice (Gregson et al. 2010).

Development of treatment goals for critical care and new sequences of care and specialty practice can improve outcomes after ICH. Specific treatment approaches include early diagnosis and hemostasis, aggressive management of blood pressure, open and minimally invasive surgical techniques to remove clots, techniques for removing intraventricular blood, and management of intracranial pressure. These approaches improve the clinical management of ICH patients, reduce mortality, and increase functional survival (Morgenstern 2010).

2.2 Introduction

Non-traumatic ICH results from the rupture of blood vessels in the brain. It is a major public health problem with an annual incidence of 10–30 per 100,000 population, accounting for 2 million (10–15%) of about 15 million strokes worldwide each year (Morgenstern 2010). Hospital admissions for ICHs have increased by 18% in the past 10 years, which is probably because of the increase in the number of elderly people, many of whom lack adequate blood pressure control and increasingly use anticoagulants, thrombolytics, and antiplatelet agents. Mexican Americans, Latin Americans, African Americans, Native Americans, Japanese, and Chinese have higher incidences of ICH than white Americans (van Asch et al. 2010). These differences are mostly seen in the incidence of deep ICH and are most prominent in young and middle-aged people. The incidence may be decreased in some populations with improved access to medical care and blood pressure control (van Asch et al. 2010).

Primary and secondary (anticoagulant-induced) ICHs have similar underlying pathological changes (Huhtakangas et al. 2011). ICH commonly affects the cerebral lobes, basal ganglia, thalamus, brain stem (predominantly the pons), and cerebellum because of the ruptured vessels due to the hypertension-related degenerative changes or cerebral amyloid angiopathy (Viswanathan et al. 2011). Most bleeding in hypertension-related ICH is at or near the bifurcation of small penetrating arteries that originate from the basilar arteries or the anterior, middle, or posterior cerebral arteries. Small artery branches of 50–700 μm in diameter often have multiple sites of rupture; some are associated with layers of platelet and fibrin aggregates. These lesions are characterized by breakage of elastic lamina, atrophy and fragmentation of smooth muscles, dissections, and granular or vesicular cellular degeneration. In particular, severe atherosclerosis, including lipid deposition, can affect elderly patients. Fibrinoid necrosis of the

subendothelium with subsequent focal dilatations (i.e., micro-aneurysms) leads to ruptures in a small proportion of patients (Takebayashi et al. 2012).

Cerebral amyloid angiopathy is characterized by the deposition of amyloid-β peptide and degenerative changes (e.g., micro-aneurysm formation, concentric splitting, chronic inflammatory infiltrates, and fibrinoid necrosis) in the capillaries, arterioles, and small- and medium-sized arteries of the cerebral cortex, leptomeninges, and cerebellum (Rosand et al. 2009). Cerebral amyloid angiopathy leads to sporadic ICH in elderly people, which is commonly associated with variations in the gene encoding apolipoprotein E, and a familial syndrome in young patients is typically associated with mutations in the gene encoding amyloid precursor protein (Rost NS 2008). White matter abnormalities (e.g., leukoaraiosis) seem to increase the risk of sporadic and familial ICHs, suggesting a shared vascular pathogenesis (Hart & Smith 2004).

ICH associated with oral anticoagulants typically affects patients with vasculopathies related to either chronic hypertension or cerebral amyloid angiopathy, which may represent an exacerbation of an existing risk of a clinical or subclinical disease (Viswanathan et al. 2011).

2.3 Pathophysiology

Regions surrounding hematomas are characterized by edema, apoptosis, necrosis, and inflammatory cells. Hematomas induce injury (Figure 2.3) by causing a mechanical disruption of the neurons and glia, followed by mechanical deformation that causes oligemia, neurotransmitter release, mitochondrial dysfunction, and membrane depolarization (Pérez et al. 2010).

Dependent on the severity of mitochondrial dysfunction, the results of injury range from temporary metabolic suppression (i.e., a hibernation phase) to cellular swelling and necrosis. A secondary cascade of injury is caused by the products of coagulation and hemoglobin breakdown, in particular thrombin, which activates microglia within 4 h after injury (Wu et al. 2013). Activated microglia release products that induce the breakdown of the blood-brain barrier, vasogenic edema, and apoptosis in the neurons and glia (Pérez et al. 2010).

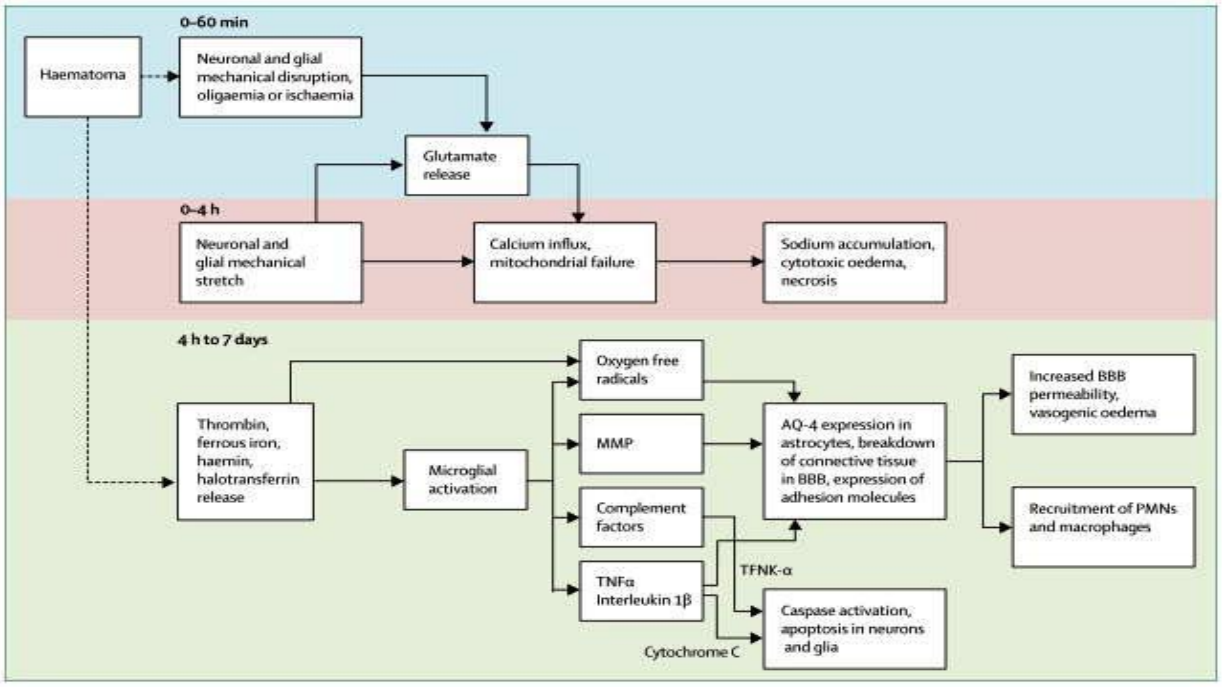

Figure 2.3: The cascade of neural injury initiated by intracerebral hemorrhages (Qureshi et al. 2009)

Hemostasis is initiated by the local activation of hemostatic pathways and mechanical tamponade. However, about 73% of patients assessed within 3 h of symptom onset have some degree of hematoma enlargement, and up to 35% have clinically prominent enlargement (Qureshi et al.

2014). Most hematoma enlargement occurs within 3 h after injury, although enlargement can occur up to 12 h after onset. Perihematomal edema increases in volume by about 75% in the first 24 h after ICH, peaking within 5–6 days and lasting up to 14 days (AI Qureshi et al. 2009). An early large edema volume relative to the hematoma volume has the greatest effect on outcome. However, even an edema that is small initially can increase in volume in the first 24 h after hemorrhage. An acute hypometabolic and hypoperfusion (hibernation) phase with mitochondrial dysfunction and metabolic failure has been reported in the region surrounding the hematoma (Qureshi et al. 2009) (Figure 2.3.i).

Regional hypoperfusion in clinical and experimental studies does not always seem severe enough to induce ischemia, and it may be secondary to hypometabolism. In the presence of very high intracranial pressure and low cerebral perfusion pressure, the risk of global ischemia is high. A variable reperfusion phase lasts from 2–14 days, and a normalization phase develops after 14 days with the re-establishment of normal cerebral blood flow in all viable regions (Kwon 2014 & Greenberg 2009).