OUTCOME OF TRAUMATIC SUBARACHNOID HAEMORRHAGE PATIENTS TREATED WITH NIMODIPINE: A TWO YEAR RETROSPECTIVE STUDY.

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Abstract

A retrospective study was done to analyse the outcome of head injury patients with traumatic subarachnoid haemorrhage (SAH) treated with out nimodipine and those receiving nimodipine treatment. Nimodipine has been used to treat aneurysmal subarachnoid haemorrhage and is currently being used for traumatic subarachnoid haemorrhage in developed countries. This study revealed a favourable outcome of patients who received nimodipine for head injuries associated when subarachnoid haemorrhage as seen on a Computed Tomographic Scan of the brain.

A retrospective analysis of 16 cases of traumatic subarachnoid haemorrhage, who were admitted during past two year to the neurosurgical service of the University Hospital Sciences Malaysia. All cases of SAH were confirmed by cranial CT Scan without Lumber puncture. Clinical parameters were evaluated using Glasgow Outcome Score(GOS) on discharge, on subsequent 3 months and followup and lastly on 48 month follow up. 6 patients were on nimodipine treatment and 10 patients received no nimodipine treatment. Each group of patient was divided into two those who had a GOS category of 1-3 and those with GOS category of 4-5. The data analysed by Fisher, exact test revealed better GOS category in the patient who received nimodipine.
Introduction

Cerebral oedema and cerebral vasospasm are two factors beside the other factors, causing secondary brain injury. Almost all of the severe traumatic brain injury leads to cerebral oedema. Subarachnoid haemorrhage is one of the cause of the intracranial hypertension and determines the outcome of head injured patients. About 54 percent of severe head injury patient exhibited an increased in an intracranial pressure of more than 20 mmHg, and an overall 50 percent of the severe head injury patient died of high intracranial pressure.

Post traumatic cerebral vasospasm, have been reported in about 39% of head injury associated with subarachnoid haemorrhage. Both cerebral oedema and vasospasm led to cerebral ischemia, which is carry a poor outcome in severe head injury patients.

Patients and methods

A retrospective analysis of sixteen traumatic subarachnoid haemorrhage over past two years were done. All cases were confirmed by cranial CT Scan. These patient’s medical report were studied on their outcome on discharge and follow-up. These patient’s were divided into two groups:- patients treated with nimodipine and without nimodipine. Each group of patient were divided once more into two groups, a) Glasgow outcome scale category of 1-3 and b) Glasgow outcome scale of category 4-5.

The data analysis were performed using the Fisher Exact Test, to identified the significant good outcome of nimodipine treated group. Variable with two-sided P value <0.01 were significant.
Result

All of patient on nimodipine treatment had a GOS category of 4-5 at one month of treatment. 40% of non-nimodipine treated patients had a GOS category of 4-5 after 48 month of treatment. 60% this group have GOS category of 1-3 after 48 months on treatment.

We found that, patients who sustained traumatic subarachnoid haemorrhage (SAH), associated with subdural haemorrhage (SDH), intracerebral haemorrhage (ICH), or extra-dural (EDH), responded well to nimodipine treatment. These patients was discharged home much earlier, and they were independent and returned to work earlier (mean: 6 months) compared to the non-nimotop group (mean: 18 months).

Discussion

Post traumatic cerebral vasospasm is an important cause of cerebral ischemia. Kakarieka A and associates reported cerebral vasospasm associated with traumatic subarachnoid haemorrhage in about 39% of cases. From this report, poor outcome in SAH (subarachnoid haemorrhage) was believed due to arterial spasm.

By Transcranial Doppler ultrasound, Martin and co-workers studied 30 head injury patient. 30% of these patient develop vasospasm. Where cerebral flow reduced to less than 30 ml per 100 gram per minute and caused poor outcome. Post traumatic cerebral spasm cases were associated with the presence of a subarachnoid clot and the mechanism thought to be similar to aneurysm induce spasm. Patient develop four between day 4 and day twenty two of post-traumatic brain injury. CT Scan findings which were performed at 72 hours of SAH was the best predictor of spasm. Subarachnoid clots greater than 3 mm in the basal cistern or layers of blood 1 mm or greater were associated with almost 100% incidence of spasm.

Monitor of proximal vessels spasm can be done by serial Transcranial Doppler ultrasound (TCD), (ICA, MCA, ACA, basilar and vertebral arteries). Increased in velocity more than 200cm/sec, especially in the MCA (middle cerebral artery), and ACA (anterior cerebral artery) correlate high with severe angiographic spasm.

Major effects of subarachnoid haemorrhage (SAH) due to accumulation of RBC haemolysis products. These mechanism leads to cerebral vasospasm and give rise to decreased in cerebral perfusion followed by cerebral ischemia. Cerebral ischemia is one of the important factors for secondary brain damage. Haemolysis of
RBC in subarachnoid spaces, causes release of oxyhaemoglobin, bilirubin, methemoglobin.\textsuperscript{11} Auto-oxydation of oxyhaemoglobin produce super-oxide radicals, which catalyst lipid peroxidation (poly-unsaturated fat) of subarachnoid clot. Lipid peroxidation progressively increases, reaching maximum effects after 5 days.\textsuperscript{1} Haemoglobin breakdown leads to increased amounts free irons, which is a powerful catalyst of free radicals reactions. Free radicals lipid peroxidation are an established aetiology or mechanism , leading to endothelial injury and activation of protein kinase C, which in turn leads to sustained cerebral vasospasm. Endothelial injury causes platelet aggregation production of eicosonoids, which is further source of free radicals through prostaglandin hydroperoxidase reactions.

In SAH, prostacylin synthesis is significantly impaired, but it is increased in the production of PGF\textsubscript{2}, thromboxane B\textsubscript{2} and PGE\textsubscript{2} which is leads to cerebral vasospasm. Oxyhaemoglobin stimulate the production of eicosonoids in cerebral arteries and acts as an inhibitors of prostacyclin, which is generated predominantly in the endothelium.

Endothelin (powerful vasoconstrictors) are produced by the endothelial cells and it’s synthesis is stimulated by oxyhaemoglobin. This will produced imbalance between increased vasoconstriction and impaired vasodilatation, and lead to delayed vasospasm.

Thick subarachnoid blood clot impaired nourishment from the adventitial surface. The cerebral vessels lack of vasa vasorum, causes of energy, causes cerebral spasms resulting in hypoxia. A direct consequence of hypoxia is the impaired function of endothelium derived relaxing factors (EDRF) or nitric oxide (NO). Oxyhaemoglobin acts as a competitive inhibitors to NO by blocking the action of NO on guanylate cyclase enzymes which leads to significant decreased in cyclin guanosine monophosphate content in the cerebral arteries after SAH. It is also possible that after SAH, NO and EDRF is deactivated by superoxide radicals with transformation into NO\textsubscript{2} and hydroxyls radicals.

With all changes in cerebral arteries, the net results is persistent cerebral vasospasms and once vasospasm is fully established than cerebral ischemia occurs.\textsuperscript{12-19}
Addition of calcium to isolated cerebral arteries leads to spasm. This effect can be inhibited by application of calcium channels blockers, such as nimodipine. Intravascular infusion of the nimodipine, which can cross blood brain barrier, has been shown to increased cerebral blood flow and improved clinical outcome. It is due to improved micro-circulation flow or may be by direct neuroprotective effect. It has no direct effect on major vessels. Spasm it is believed that, nimodipine dilates small parenchymal vessels as well as leptomeningeal collateral arteries. Prophylactic treatment with nimodipine at a dose of 60 mg every 4 hours, starting at diagnosis and continued for 21 days, is recommended. Nimodipine has the side effects of reducing peripheral resistance, which is leads to hypotension and reduce cerebral perfusion pressure may results for some patients. This effect can be reduced or minimised by maintaining adequate intra-vascular volume, or dividing the dose to 2 hours intervals, or by concomittent administration of pressors, especially during symptomatic vasospasm.
Table 1
Glasgow Outcome Scale

1. death
2. Persistent vegetative state* No awareness of themselves or environment due to severe bilateral hemispheric damage.
3. Severe Disability Dependent for some support in every 24 hour period.
4. Moderate Disability Dependent but disabled. May or may not be capable of return to work.
5. Good Recovery Good, but not necessarily complete recovery. e.g cranial nerve deficit. Could (although may not) return to work.

Table 2
Fisher Exact Test.

<table>
<thead>
<tr>
<th>Group</th>
<th>G.O.S 24 months after treatment of S.A.H in HUSM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>G.O.S (4-5)</td>
</tr>
<tr>
<td>SAH + no nimodipine</td>
<td>4(A-a)</td>
</tr>
<tr>
<td>SAH with nimodipine</td>
<td>6(B-b)</td>
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Test statistic is no observed value b as shown in the above table.
Distribution of test is by referring to table. Statistical table.

Decision rule. Suppose we let @ = 0.01. The decision, then, is to reject null hypothesis (Ho) if the observed value of b is equal to or less than 0, the value of b on statistical table for A=10, B=6, A=6, and @ = 0.1

Calculation of test statistic. The observed value of b, as shown in statistical table is 0.

Statistical decision. Since 0=0, we reject the null hypothesis (Ho)

Conclusion. Since we reject Ho, we conclude that the probability of good outcome is much higher in a patients of group SAH treated with nimodipine than in a group of SAH patient without nimodipine.
References


