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## Clopidogrel and Aspirin Combination in Transitory Ischemic Attack and Acute Minor Stroke

Thirty percent of the cerebrovascular incidents consist of either minor strokes or transient ischemic attacks (TIA). 10-20% of the patients have a stroke within the next 3 months of such ischemic events. Most of the repeating events take place within the next 2 days. As long as there is no visible cardiac basis in the secondary prophylaxis of these patients, aspirin and clopidogrel is often used in combination. Multiple studies on combination treatments showed that, as opposed to coronary events, aspirin and clopidogrel combination is not superior to monotherapy (1, 2, 3). These studies have been criticized for including predominantly medium-high severity stroke cases and excluding the early stage where stroke recurrence is more frequent.

Wang et al.'s study titled "Clopidogrel in High Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE)" published in *New England Journal of Medicine* this year tested the efficiency of combined antiaggregant treatment in preventing early stage recurrence (4). Researchers assigned 5170 patients reporting with TIA and minor ischemic stroke (NIH stroke score <4) in 114 centers in China into 2 random groups of equal size within 24 hours. Both groups received 75-300 mg aspirin in the first day. The combination treatment group started on 300 mg clopidogrel after the second day and kept taking 75 mg/day for 90 more days while also taking 75 mg/day aspirin for 21 days. After the 21st day, aspirin treatment was changed to placebo. In the aspirin group, patients received 75 mg/day aspirin treatment for 90 days and placebo instead of clopidogrel. The primary efficacy outcome was defined as the comparison of a incidence rate of a new stroke event at 90 days between group. The second efficacy outcome was the comparison of groups in terms of other new vascular events such as hemorrhagic stroke, myocardial infarction or vascular death.

The mean age of the patients was 62 and 1/3rd of them were male. Sixty six percent had hypertension, 22% had diabetes and 43% were smokers. Transient ischemic attack patients constituted 28% of the sample.

In the results, 8% of the patients who received combined treatment had stroke versus 12% of the patients who took aspirin alone ( $p<0.001$ ). Five percent of the combined treatment group versus 7% of the aspirin alone group had stroke that was fatal or severely debilitating ( $p=0.01$ ). Hemorrhagic stroke was seen with 0.03% in both groups and the groups did not differ significantly. Any other causes of fatality was not found to be significantly different between the groups.

In summary, using aspirin and clopidogrel combined treatment starting in the first 24 hours of TIA and minor stroke and continuing for 3 weeks, and then using clopidogrel alone reduces the stroke risk by 32% compared to aspirin alone treatment. The fact that this study recruited patients with low hemorrhagic transformation and high recurrence risks can suggest that the effect of combination treatment here might be amplified, as opposed to similar studies conducted previously. In addition, it should be noted that 3-week combination treatment did not increase the hemorrhage risk.

## References

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## Thrombocytopenia as an Outcome Predictor in Acute Encephalitis

Even though there are tens of infectious and autoimmune causes for encephalitis, the etiology in 50% of the patients cannot be detected with certainty. Commonly resulting in severe debilitation, the factors determining the progression and outcome of this condition are often vague and unreliable. Thakur et al.'s study published in *Neurology* this year compared the parameters predicting the outcome of the encephalitis patients in ICU (1). In this retrospective study, the researchers looked at the acute encephalitis cases admitted in John Hopkins University Hospital between the years 1997-2011.

In the study, encephalitis diagnosis is made if the patient satisfied at least 2 of the following conditions: encephalopathy described as change in conscious state or personality for longer than 24 hours, fever, seizure, focal neurological deficit, CSF pleocytosis or EEG/neuroimaging findings compatible with encephalitis. Patients older than 16 years old and who spent longer than 48 hours in the ICU were included in the study. The ones with delirium conditions and encephalopathies due to sepsis, toxins or metabolic causes were excluded from the study.

Hundred and three patients were divided into 4 groups: viral, nonviral infectious (due to bacterial or fungus infection), autoimmune or undetermined cause encephalitis.

The mean age of the patients was 52 with balanced gender distribution. Twenty three percent of the patients were over 65 years old and 30% were immunosuppressed. Twenty seven percent was viral, 9% nonviral infectious, 16% autoimmune and 46.6% was encephalitis with unknown cause. Herpes simplex was seen to be the most common cause of encephalitis with 16%. In the first consultation, 37% of the patients were under 8 points in the Glasgow coma scale. The mean duration for hospital stay was 26, and ICU stay was 13 days. Thrombocytopenia developed in 22%, status epilepticus in 18%, and cerebral edema in 15% of the patients.

Eighteen percent of the patients died and the most common causes of fatality according to multiparametric regression analyses were cerebral edema, status epilepticus and thrombocytopenia. The mean age of 65 years, immunosuppressed state and comorbid disorders possibly also contributed to the fatality rate but these factors were not found to be statistically significant. Modified Rankin scores of the discharged patients was 0-3 in 36% and 4-5 in 56%. The cases who needed ventilator and those with autoimmune-related encephalitis progressed much worse to other patients.

In summary, the researchers established the relationship of fatality with cerebral edema and status epilepticus. Cerebral edema stands out as the most strongly associated cause of mortality.

Another interesting finding in the study was that thrombocytopenia seen in 1/3rd of the critical patients had an independent predictive power in the outcome of the encephalopathy. Past studies with intensive care patients suggest thrombocytopenia as a powerful predictor in mortality. In these patients, the cause of thrombocytopenia is often bone marrow suppression, peripheral platelet destruction, splenic sequestration or hemodilution due to blood loss.

In conclusion, the short term debilitation rates of autoimmune encephalitis seem to be higher than those caused by other etiologies. Furthermore, thrombocytopenia stands out as an important prognostic marker. Despite these striking findings, the retrospective nature of the study and the failure to report on the long-term prognosis still diminishes the saliency of the results.

## References

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## Valproate Use as a First Choice in Status Epilepticus

Drug preferences for status epilepticus (SE) are undergoing a change with the availability of intravenous version valproate in addition to the new generation antiepileptics. Numerous studies showed that valproate can be used as an effective alternative to lacosamide, levetiracetam and topiramate phenytoin in the treatment of SE. A meta-analysis of 5 studies investigating valproate, which is the oldest of these drugs, showed the high effectiveness of this drug (1). In addition, valproate does not cause adverse cardiovascular effects like cardiac arrhythmia and hypotension as opposed to phenytoin.

In the study by Tiamkao et al. published in *BMC Neurology* this year, the outcomes of SE patients who used either phenytoin or valproate (2). The study included patients over 15 years old from Khon, Srinagarind Hospital in Thailand between the years 2003-2010. The primary drug choice for these patients were either phenytoin or sodium valproate. All patients received 10 mg iv diazepam as initial treatment. Treatment results were compared in terms of success rate in seizure control, time elapsed until establishing control, post-treatment functionality and fatality.

Seventeen out of 37 patients received phenytoin and 20 received iv valproate treatment. Both groups seemed to be similar in terms of basal demographic and clinical properties. In either groups, a quarter of the patients needed two or more antiepileptic treatment during SE treatment. Phenytoin's mean loading dosage was 743 mg with a speed of 20 mg/min while valproate's loading dose was 1000 mg with a speed of 26 mg/minutes. After the loading treatment, the maintenance dose was determined as 300 mg/day for phenytoin and 1200 mg/day for valproate. While the groups did not show any visible clinical changes, seizure control time, hospital stay and functional outcome rates were better in the valproate group.

Even though the study did not have a randomized design and had low statistical power due to small sample size, the findings suggest that iv valproate is not any less effective than iv phenytoin in the treatment of SE. In addition, it is noteworthy that sodium valproate performed more favorably in certain clinical outcome parameters. Further clinical studies with properly randomized designs are needed to support these findings.

## References

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