Comparison between Aspirin Combined with Dipyridamole versus Aspirin Alone within 48 Hours after Ischemic Stroke Event for Prevention of Recurrent Stroke and Improvement of Neurological Function : A Preliminary Study

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Objectives: *To determine efficacy and tolerability of aspirin plus dipyridamole (combination) versus aspirin alone in acute intervention treatment after acute ischemic stoke among Thai patients.*
Material and Method: *This pilot study enrolled ischemic stroke patients within 48 hours and randomized to aspirin 300 mg/d or combination (aspirin 300 mg/d+ standard release dipyridamole 75 mg thrice a day) and followed up for 6 months. End points were recurrent ischemic stroke, transient ischemic attack and vascular death. Side effects were recorded. National Institutes of Health Stroke Scale was assessed at entry and at 6 months period for determining neurological functions.*
Results: *Of 38 patients, mean age was 64.3 years. Male and female were 52.6% and 47.4% respectively. There were 18 patients in the aspirin group and 20 patients in the combination group. No patient developed end point events or no significant adverse event in both groups. The combination group showed more improvement in neurological function than the aspirin group (p-value 0.009).*
Conclusion: *This pilot study showed equal efficacy and tolerability of the combination group and aspirin alone in acute intervention treatment for prevention of recurrent stroke or vascular death within 6 months.*

Keywords: *Aspirin, Dipyridamole, Prevention, Acute intervention*

J Med Assoc Thai 2005; 88(Suppl 3): S148-54
Full text. e-Journal: *http://www.medassocthai.org/journal*

Cerebrovascular disease is an important condition and is the leading cause of mortality and morbidity in the elderly, either ischemic or hemorrhagic stroke[1-4]. Until now, increasing pathophysiologic knowledge and novel therapies for acute ischemic stroke has changed the management of stroke patients. Brain damage occurs after intracranial arterial occlusion and produces various focal neurological dysfunction. In late treatment or inadequate reperfusion, irreversible brain damage may occur[5,6]. Acute management of ischemic stroke has been revolutionized over the past decade. Reperfusion therapy can rescue tissue which is functionally inactive but still viable (ischemic penumbra). The result of two large randomized, non-blinded acute interventional studies indicated that aspirin 150-300 mg given within 48 hours after ischemic stroke can reduce mortality and rate of recurrence of ischemic stroke[7-9]. All other remaining antiplatelet trials are secondary prophylaxis. Most of them enrolled within 3-6 months after the onset. Antiplatelets that have benefit shown in secondary prophylaxis trials are aspirin, ticlopidine, clopidogrel and aspirin plus dipyridamole, whereas antipletelet that has data in acute intervention is only aspirin[10-12]. The second European stroke pre-

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vention study in 1996 showed that dipyridamole modified release formulation 200 mg combined with aspirin 25 mg given twice daily was effective in secondary prevention of stroke and transient ischemic attack (TIA) when compared with aspirin or dipyridamole (DP) alone. The authors aimed to prove efficacy of aspirin plus dipyridamole in acute intervention treatment within 48 hours after onset of acute ischemic stroke for prevention of ischemic stroke, TIA, vascular death, improvement of neurological functions and tolerability of this combined regimen comparison with aspirin 300 mg daily alone among Thai patients.

Material and Method

Patients recruitment and eligibility

From September, 1st, 2003 to May, 31st, 2004, the authors enrolled patients from the neurological division, Department of Medicine, Phramongkutklao Hospital who were diagnosed with acute ischemic stroke within 48 hours after clinical onset. Patients were eligible for inclusion in the present study if they were more than 45 years old, imaging by computer tomography (CT) or magnetic resonance (MR) of the brain confirmed cerebral infarction and excluded hemorrhagic stroke or brain tumor. The exclusion criteria were atrial fibrillation or high risk of cardio-embolism, valvular heart disease, history of dyspepsia, bleeding tendencies, internal organ bleeding within 1 year, had previous antiplatelets or anticoagulant, severe co-morbid or life threatening conditions such as unstable vital signs, sepsis, cancer, HIV infection, SLE, pregnancy, polycythemia vera, bed ridden, dementia, previous stroke within 1 year, Glasgow coma score < 8, or on a respirator. Medical and neurological history and examinations were recorded. The present study was approved by the ethical committee and patients who were eligible gave written consent.

Procedures

The present study was a pilot project, and the authors planned to recruit 30-40 patients entry to the present trial. The authors used the Oxfordshire community stroke project classification (OCSP)[13] to classified type and size of ischemic stroke before randomization. Treatment group allocation was determined by an open label, blind assessed randomization system. Randomization distributed patients equally among the following two treatment groups: aspirin 300 mg daily versus the combination of aspirin 300 mg daily and standard release dipyridamole (DP) 75 mg three times per day. Treatment was started on the day of randomization and continued for six months. Follow up visit was scheduled on 1, 3 and 6 months after entry. At each visit, patients were systemically questioned regarding primary and secondary end points and adverse events. Primary end points of the present study were recurrent ischemic stroke and TIA. Secondary end points were vascular death either from myocardial infarction or any type of stroke. Adverse event questionnaire included fatal and non-fatal adverse events such as dyspepsia, bleeding problems, headache, skin reaction and other complaints by the patients. The US National Institute of Health Stroke Scale (NIHSS) was assessed at entry and 6 months follow up period for determining neurological function. The increasing of NIHSS represented worsening, whereas reduction represented improvement [14-16].

Statistical analysis

The continuous data were assessed by means and standard deviation (SD) and discrete data were assessed by percent. Analysis was based on the first occurrence of an event in the primary or secondary endpoint during the follow up period. The efficacy analysis between groups was evaluated from prevalence of end point events and changing of NIHSS. The authors used t-test, chi-square test, analysis of covariance (ANCOVA) and used p-value<0.05 for statistical significance. Statistical analysis was assessed by the statistic program, SPSS version 11.5.

Results

During nine months of the screening period, the authors recruited 39 from 60 eligible patients into the present study. The diagram of patients is shown in Fig. 1. At the entry period, the authors excluded 1 patient who was newly diagnosed with lung cancer, so 38 patients were enrolled for study. In overall patients, mean age was 64.3 years (range 45-77, SD 9.6), male 20 patients (52.6%), female 18 (47.4%). According to the OCSP classification; the size of stroke was small vessel stroke in 28 patients (73.7%) and large vessel stroke in 10 patients (26.3%). In large size stroke, three patients had aphasia. The ischemic insult were carotid circulation in 32 patients (84.2%) and vertebrobasilar system in 6 patients (15.8%). Regarding the common risk factors of ischemic stroke in the present study, were hypertension (50%), current smoking (34.2%), DM (31.6%) and dyslipidemia (18.4%). Underlying ischemic heart disease was 7.9%. Previous ischemic stroke patients that had developed in more than 1 year were 5.3%.

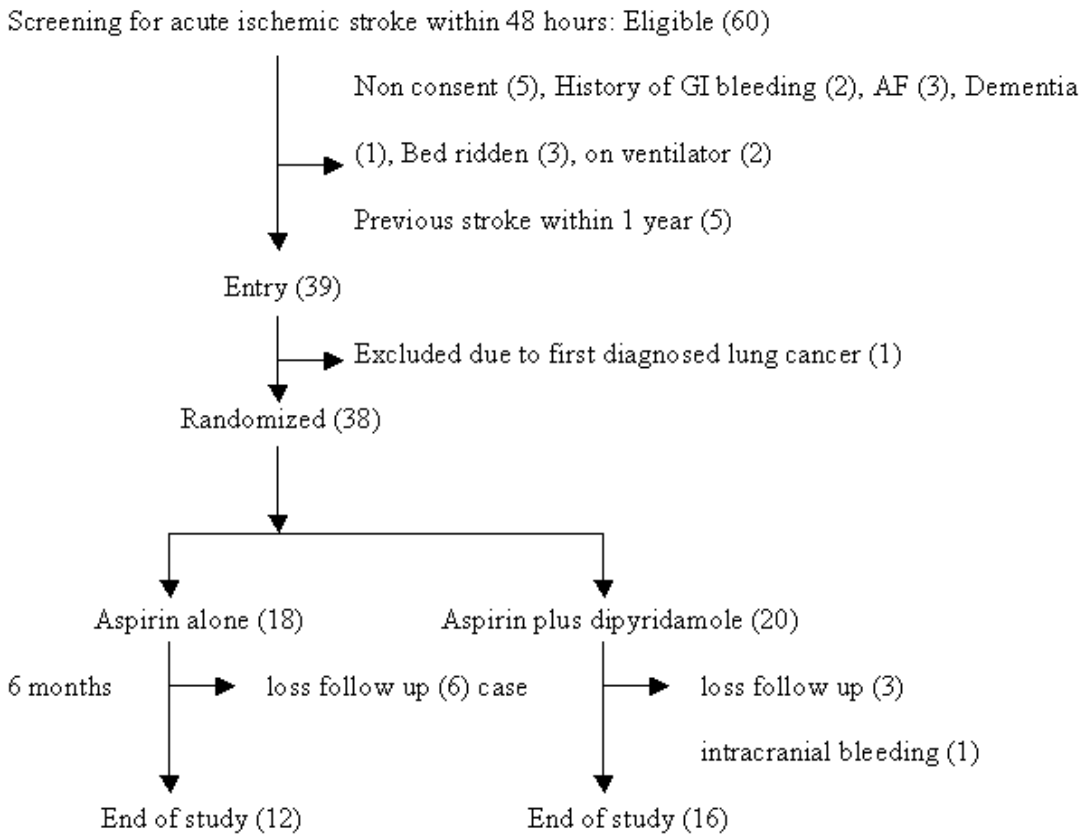

Fig. 1 Study diagram

The patients were randomized into 2 groups (aspirin alone or aspirin + DP). There were 18 allocated in the aspirin group (47.4%) and 20 in the combination group (52.6%). The demographic characteristics in both groups were similar and there was no statistical significant difference between the groups including age, sex, vascular site, infarct size, smoking, alcoholic drinking, DM, dyslipidemia, ischemic heart disease and initial NIHSS. But a larger number of hypertension was found in the combination group. The mean NIHSS were 8.12 and 6.25 respectively (no statistical significant difference). The details of demographic characteristics are demonstrated in Table 1.

After 6 months follow up, available data was 28 patients (73.7%), according to 1 patient (2.6%) who developed a severe adverse event that required cessation of treatment and 7 (18.4%) lost to follow up. The authors compared the demographics between the groups of lost to follow up and those remaining in the present study and found that both had no difference in clinical demographics. One patient in the combination group developed a major adverse event 3 days after onset of stroke or 2 days after being enrolled (intracranial bleeding). This patient was a 72 year-old-man who had hypertension, dyslipidemia, current smoking, alcoholic drinking and developed hemiparesis and aphasia from large carotid circulation stroke. After stopping medication and conservative treatment, he survived with neurological deficits. No patient developed both primary or secondary end point events either recurrent stroke & TIA or vascular death in both groups. Only 1 patient who got combination therapy complained about throbbing headache that subsided after conservative treatment by a short course of simple analgesic and there was no recurrence. No patient in both groups developed dyspepsia or other internal organ bleeding. Of 26 patients that the authors could assess NIHSS at the 6th month, none of them showed an increase of NIHSS or worsening of stroke. Some patients had the same score but most of the patients had score reduc-

Table 1. Demographic characteristics before entry

Baseline and stroke	Initial enrolled patients			Remained patients at 6 months		
Characteristic	aspirin N (%)	aspirin+DP N (%)	p value	aspirin N (%)	aspirin+DP N (%)	p value
Mean age [years (SD)]	64.5 (2.4)	64.4 (2.2)	0.995	60.8 (10.3)	62.6 (10.2)	0.656
Male: female (case)	8 : 10	12 : 8	0.338	4 : 7	9 : 7	0.310
DM	6 (33%)	6 (30%)	0.83	5 (41.7%)	3 (20 %)	0.144
Hypertension	5 (38.5%)	14 (70%)	0.009 *	3 (25%)	10 (66.7 %)	0.079
Dyslipidemia	1 (6%)	6 (30%)	0.052	1 (8.3%)	4 (26.7 %)	0.302
IHD	2 (11%)	1 (5%)	0.49	2 (16.7 %)	1 (6.7 %)	0.357
Old CVA	0 (0%)	2 (10%)[a]	0.168	0 (0%)	1 (6.7 %)	0.593
Current smoking	6 (33.3%)	7 (35%)	0.914	4 (33.3 %)	4 (26.7 %)	0.414
Alcohol	5 (27.7%)	6 (30%)	0.88	4 (33.3%)	3 (20 %)	0.279
Small vessel stroke	13 (72%)	15 (75%)	0.846	9 (75 %)	13 (86.7%)	0.684
Large vessel stroke	5 (28%)	5 (25%)	0.846	2 (16.7 %)	3 (20 %)	0.684
Carotid stroke	13 (72%)	19 (95%)	0.055	8 (66.7 %)	16 (100%)	0.027*
Vertebrobasilar stroke	5 (28%)	1 (5%)	0.055	3 (25%)	0 (0 %)	0.027*
Mean NIHSS: score (SD)	8.12 (6.9)	6.25 (3.7)	0.31	8.9 (7.8)	6.75 (3.9)	0.347
Total (case)	18	20	-	12	16	-

NB: DP = dipyridamole,
DM = diabetes mellitus, CVA = cerebrovascular disease, DP = dipyridamole,
IHD = ischemic heart disease
NIHSS = national institute of health stroke scale, SD = standard deviation
* significant p-value < 0.05
[a] old cerebrovascular disease > 1 year

Table 2. Mean score of NIHSS in study group

Mean (SD) of NIHSS	aspirin	aspirin + DP	p-value	All group
At entry (n = 38)	8.12 (6.9)	6.25 (3.7)	0.31	6.97 (5.4)
At 6 months (n = 26)	5.36 (5.2)	2.06 (2.9)	0.052	3.46 (4.3)
Reduction in 6 months	3.31 (3.2)	4.24 (1.9)	0.009[b]	3.83 (2.6)

[b] analyzed by analysis of covariance (ANCOVA)
DP = dipyridamole
SD = standard deviation

tion that represented improvement of neurological function. The sequence of mean NIHSS of entry and at 6 months in overall patients were 6.97 and 3.46 respectively. Mean score of NIHSS at entry/at 6 months follow up of aspirin was 8.12/5.26 and aspirin + DP was 6.25/2.06. Comparison of reduction in NIHSS between aspirin and aspirin + DP showed improvement of neurological function in combination group more than aspirin alone. By ANCOVA, the authors found more reduction of NIHSS in the combined group than aspirin alone with p value 0.009. The details of NIHSS are shown in Table 2. By univariate analysis, the factor which determined reduction of NIHSS was a size of the ischemic stroke [large vessel stroke had a higher score reduction than small vessel stroke (p value 0.008)].

Discussion

According to previous antiplatelet treatment trials of acute intervention in acute ischemic stroke,

aspirin is the most widely studied antiplatelet agent and, until recently, aspirin was the only drug used broadly for this purpose. Aspirin interferes with platelet function and thromboxane A_2 production by irreversible acetylation and inactivation of isoform 1 of the cyclo-oxygenase enzyme (COX-1). Dipyridamole increase the concentration of cyclic guanosine monophosphate (cGMP) in the platelet by inhibiting phosphodiesterase, stimulating prostacyclin production, and reducing cellular uptake of adenosine, as well as inhibiting the oxidation of LDL. When used alone, dipyridamole has shown antiplatelet effects similar to those of low dose aspirin. Combination therapy with aspirin and dipyridamole may be beneficial because they affect platelets through different mechanisms.

The authors aimed to prove the efficacy of aspirin + DP comparison with aspirin alone in acute intervention treatment of ischemic stroke. The authors used 300 mg of aspirin based on the previous trial that had an improved outcome of stroke in acute intervention therapy[7-9]. According to no sustained release formulation (200 mg/tablet) of DP in Thailand at the time of the present study, the authors used standard release of dipyridamole with the dosage of 75 mg in this pilot study. However, the authors did not find a statistical significant difference between the groups, including recurrent stroke, TIA, vascular death and adverse events that might be due to the small sample size. There was improvement of neurological function in the combination group at 6 months compared with aspirin alone. The different baseline characteristic between groups in the remaining patients at 6 months was more vertebrobasilar stroke in the aspirin group and more carotid stroke in the combination group. However, the authors didn't find the effect of this difference on the outcome, so the improvement of neurological dysfunction might be due to the effect of the drug used. Although, the authors found statistical difference in reduction of NIHSS, clinically there was no striking difference. Adverse events of this trial were one patient with headache and one with intracranial bleeding only in the combination group but there was no statistical significant difference. The intracranial bleeding was hemorrhagic transformation of ischemic stroke. This was a major adverse event that might be caused by the studied drugs or natural history of a large infarction, however, the authors should be aware of this side effect when using this combination drug in a large stroke within 48 hours. Loss of follow up and excluded patients were 10 cases [(26%) from the aspirin group 6 cases and aspirin + DP 4 cases], however, the demographic data of the remaining patients were not different between groups (Table 1). The limitations of the present study were small sample size, short follow up time and many lost to follow up.The present study was only a pilot study, so the further large trial should be done.

Conclusion

In this pilot study,there was no statistical significant difference in efficacy and safety of aspirin 300 mg daily versus aspirin 300 mg daily plus standard release dipyridamole 75 mg three time a days in aspect of acute intervention treatment for prevention of recurrent stroke or TIA or vascular death in the duration of 6 months. The combination group showed more improvement of neurological function than the aspirin group.

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การเปรียบเทียบระหว่างการใช้ยา Aspirin ร่วมกับยา Dipyridamole เทียบกับยา Aspirin เพียงชนิดเดียว ภายใน 48 ชั่วโมงหลังเกิดโรคอัมพาตจากสมองขาดเลือด เพื่อป้องกันการเกิดอัมพาตซ้ำและการลดลงของอาการแสดงความผิดปกติทางระบบประสาท (การศึกษานำร่อง)

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วัตถุประสงค์: *คณะผู้วิจัยต้องการศึกษาประสิทธิผลและผลข้างเคียงของการรักษาด้วยยา aspirin ร่วมกับ dipyridamole เปรียบเทียบกับ aspirin เพียงตัวเดียว ในการป้องกันการเกิดอัมพาตซ้ำและประเมินอาการแสดงทางระบบประสาทในผู้ป่วยไทยที่มีโรคอัมพาตจากสมองขาดเลือดเฉียบพลันภายใน 48 ชั่วโมง*

วัสดุและวิธีการ: *ศึกษานำร่องจากผู้ป่วยโรคสมองขาดเลือดภายใน 48 ชั่วโมง สุ่มการรักษาด้วย aspirin 300 มิลลิกรัม/วัน หรือ aspirin 300 มิลลิกรัม/วัน ร่วมกับ dipyridamole 75 มิลลิกรัม 3 เวลาต่อวัน (กลุ่มยารวม) ติดตามเป็นเวลา 6 เดือน จุดสิ้นสุดการศึกษาคือ มีการเกิดอัมพาตจากสมองขาดเลือดซ้ำ, transient ischemic attack และการตายจากโรคหลอดเลือด บันทึกผลข้างเคียงของยา ประเมินอาการแสดงทางระบบประสาทด้วย National Institutes of Health Stroke Scale เมื่อแรกเข้าการศึกษาและ 6 เดือนหลังรักษา*

ผลการศึกษา: *ผู้ป่วย 38 คน อายุเฉลี่ย 64.3 ปี เป็นเพศชายและเพศหญิง ร้อยละ 52.6% และ 47.4% ตามลำดับ ผู้ป่วย 18 คนได้รับ aspirin และ 20 คนได้รับยารวม ในระยะเวลา 6 เดือนไม่พบผู้ป่วยเป็นอัมพาต หรือเสียชีวิตจากทั้ง 2 กลุ่ม ผลข้างเคียงจากยาไม่พบความแตกต่างระหว่างกลุ่ม ในกลุ่มยารวมพบการดีขึ้นของอาการแสดงทางระบบประสาทมากกว่ายา aspirin ชนิดเดียว (p 0.009)*

สรุป: *การศึกษานี้แสดงผลเท่าเทียมกันทั้งประสิทธิภาพและการทนยา ในการป้องกันการเกิดอัมพาตซ้ำและการตายจากโรคหลอดเลือดภายใน 6 เดือน ระหว่างกลุ่มที่ใช้ยารวม เทียบกับยา aspirin ตัวเดียว ที่เริ่มการรักษาภายใน 48 ชั่วโมงหลังเกิดอัมพาต*