THE EFFICACY AND SAFETY OF CILOSTAZOL IN SUBARACHNOID HEMORRHAGE. A META-ANALYSIS OF RANDOMIZED AND NON RANDOMIZED STUDIES

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DISCLOSURE

• I have no actual or potential conflict of interest in relation to this program/presentation
OBJECTIVE

To assess the effectiveness of cilostazol, a selective inhibitor of phosphodiesterase type III, in preventing cerebral ischemia related to cerebral vasospasm after aneurysmal subarachnoid hemorrhage (SAH)
BACKGROUND

- Moderate to severe angiographic cerebral vasospasm occurs in almost 47% and results in clinical symptoms in 38% of patients with aneurysmal subarachnoid hemorrhage in recent studies.

- Death or disability was seen in 58% of patients who developed moderate to severe vasospasm in the CONSCIOUS-1 study.

- The American Heart Association/American Stroke Association guidelines state that oral nimodipine is the only agent that has been shown to improve neurological outcomes (but not cerebral vasospasm) in patients with aneurysmal subarachnoid hemorrhage (Class I; Level of Evidence A).
CILOSTAZOL

- Cilostazol, a phosphodiesterase III inhibitor, reduced cerebral vasospasm and cerebral ischemia in patients with subarachnoid hemorrhage in experimental studies and small clinical studies presumably by multiple mechanisms including:
  - Increased nitric oxide (NO) levels derived from endothelial cells
  - Inhibition of vascular smooth muscle proliferation
  - Suppression of adhesion molecule expression on vascular membrane
  - Inhibition of platelet derived growth factor (PDGF) production
We performed a meta-analysis of both randomized and non-randomized studies which investigated the therapeutic effect of cilostazol in aneurysmal subarachnoid hemorrhage.

Computerized literature search of MEDLINE and Cochrane databases on December 2nd 2017, with the following search terms: “clinical trials,” “randomized studies,” “non-randomized studies,” “cilastazol,” “subarachnoid hemorrhage,” and “standardized medical management”
Studies included in qualitative synthesis (N=6)

Eligibility

Included

Full text articles excluded, Effect of cilostazol on hydrocephalus in SAH (N=1), secondary stroke prevention (N=9), effect on vasospasm in healthy population (N=1), no control group (N=1), letter to editor (N=1)
DATA EXTRACTION

- Two authors (AI and AP) independently performed the literature search

- Data from the articles included in this study were extracted by two independent authors (MFI and SS) using a standardized form

- Following data was collected: name of the first author, publication year, study period, baseline characteristics of patients, and number of patients and rates of outcomes of interest in each group
<table>
<thead>
<tr>
<th>Trial name</th>
<th>Type of Study</th>
<th>Eligibility criteria</th>
<th>Treatment with cilostazol</th>
<th>Aneurysm Rx (clip/coil)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matsuda et al</td>
<td>RCT</td>
<td>Age 20–80 years. Anterior and posterior circulation. SAH should be diffuse on CT scan performed within 24 h of SAH. Clinical grade evaluated by Hunt and Hess grade was grades 1–4 before clipping or coiling</td>
<td>100 mg twice per day and continued for 14 days</td>
<td>126/22</td>
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<tr>
<td>Senbokuya et al</td>
<td>RCT</td>
<td>Aneurysmal SAH in anterior circulation. Hunt and Kosnik Grades I to IV</td>
<td>100 mg twice per day for 2 weeks, was started by 96 hours after the onset of SAH and by 48 hours after surgery</td>
<td>109/0</td>
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<tr>
<td>Suzuki et al</td>
<td>RCT</td>
<td>SAH in both anterior and posterior circulation. Aneurysm treatment by clipping within 72 hours of SAH. Hunt and Hess grade was grades 1–4. mRS score less than or equal to 2 prior to ictus</td>
<td>100 mg twice per day for 2 weeks after SAH</td>
<td>100/0</td>
</tr>
<tr>
<td>Yoshimoto et al</td>
<td>Non randomized</td>
<td>SAH in both anterior and posterior circulation. Aneurysm treatment by clipping or coiling early after the SAH onset (did not specify the duration, within couple of days). Hunt and Kosnik Grades I to IV</td>
<td>200 mg/d from day one after surgery for 2 weeks</td>
<td>41/9</td>
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<tr>
<td>Kimura et al</td>
<td>Non randomized</td>
<td>Aneurysm treatment by clipping within 72 hours of SAH</td>
<td>Cilostazol 100 mg orally bid. for 14 days plus combined enteral and parenteral nutrition</td>
<td>130/0</td>
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<tr>
<td>Murahashi et al</td>
<td>Non randomized</td>
<td>Aneurysm treatment by clipping within 72 hours of SAH</td>
<td>200 mg/d from day one after surgery for 2 or 4 weeks</td>
<td>81/0</td>
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<tr>
<td>Trial name</td>
<td>Definition of symptomatic vasospasm (sVS)</td>
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<tr>
<td>Matsuda et al</td>
<td>Development of new, focal neurological signs, deterioration in level of consciousness of at least 2 points on the Glasgow Coma Scale, or both, when the cause was felt to be ischemia attributable to vasospasm after other possible causes of worsening had been excluded</td>
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<tr>
<td>Senbokuya et al</td>
<td>Development of a new focal or global neurological deficit or deterioration of at least 2 points on the Glasgow Coma Scale, which was not explained by initial hemorrhage, rebleeding, hydrocephalus, surgical complications, fever, infections, or electrolyte or metabolic disturbances regardless of cerebral infarctions on CT scanning or MRI and angiographic vasospasm on DSA or CTA</td>
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<tr>
<td>Suzuki et al</td>
<td>Development of any unexplainable neurological deterioration other than rebleeding, intracerebral hematoma, hydrocephalus, brain edema, seizures, and metabolic disturbances such as hypoxia and hyponatremia. At least, CT scan was performed to exclude other pathological conditions. MR angiography, CT angiography, transcranial color sonography, and/or digital subtraction angiography were performed, if the surgeon thought it was necessary</td>
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<tr>
<td>Yoshimoto et al</td>
<td>Transient symptoms:[Cilostazol group] defined as aphasia (two patients), right hemiparesis (one patient), consciousness disturbances (one patient).[control group] confusion, aphasia, and right hemiparesis. Persistent symptoms:[Cilostazol group] aphasia.[Control group] deterioration of disturbed consciousness, aphasia, right hemiparesis, and agnosia</td>
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</table>
PRIMARY ENDPOINT

- Incidence of cerebral ischemia related to vasospasm

SECONDARY ENDPOINTS

- Angiographic vasospasm
- New cerebral infarct
- Mortality
- Poor functional outcome defined by modified Rankin scale ≥ 3 at discharge, 1, 3, or 6 month follow up
• Risk ratios (RRs) and 95% confidence intervals (CIs) were calculated using Comprehensive Meta-Analysis

• The pooled Relative risks were estimated using a random-effects model using the method described by DerSimonian and Laird

• We assessed heterogeneity and the magnitude of heterogeneity for each specific end point using the Cochran Q statistic and the $I^2$ measure (the percentage of total variability due to true between-study heterogeneity), respectively
• Proportion of subjects in which risk of cerebral ischemia related to vasospasm was significantly lower in patients which were treated with cilostazol (RR = 0.43; 95% CI 0.31-0.60; p< 0.001)
The proportion of aneurysmal subarachnoid hemorrhage patients who had new cerebral infarct were significantly lower in subjects assigned to cilostazol treatment (RR 0.33, 95% CI 0.20-0.54, p<0.001)
The proportion of aneurysmal subarachnoid hemorrhage patients who had Modified Rankin scale \( \geq 3 \) were significantly lower in subjects assigned to cilostazol treatment (RR 0.59, 95% 0.44-0.89, p=0.04)
RESULTS

Angiographic vasospasm
(RR 0.67, 95% CI 0.51-0.84, p = .001)

Mortality
(RR 0.64, 95% CI 0.15-2.76, p=0.55)

Cilostazol efficacious
Risk ratio
0.67, 95% CI 0.51-0.84

Cilostazol not efficacious
Risk ratio
0.64, 95% CI 0.15-2.76
LIMITATIONS

• No standard definition of clinical or angiographic vasospasm
• CTA instead of DSA was mostly used to diagnose vasospasm which tends to underestimate the vasospasm as well
• Selection bias with exclusion of high grade Hunt and Hess subarachnoid hemorrhage in some studies
• Majority of SAH received clipping for the treatment of aneurysm
• Screening test used in some studies was CT head instead of MRI head which would underestimate the cerebral infarction detection
CONCLUSION

- SAH patients who received cilostazol had significantly decreased incidence of sVS, angiographic vasospasm, vasospasm related new cerebral infarction and poor functional outcome although it did not show significant mortality benefit with cilostazol in SAH patients.

- However, further larger randomized controlled trials in non Japanese population with more frequent use of endovascular procedure i.e coiling of aneurysm are needed to confirm these conclusions.
Zeenat Qureshi Institutes 2018—Thank you

St. Cloud, Minnesota, USA

Donka National Hosp, Conakry, Guinea

PingAn Hosp, Shijiazhuang, China

Xuan Wu Hosp, Beijing, China