Cilostazol Prevents Cerebral Vasospasm After Aneurysmal Subarachnoid Hemorrhage: A Multicenter Prospective, Randomized, Open-label Blinded Endpoint Trial

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Introduction

Cerebral vasospasm following aneurysmal subarachnoid hemorrhage (SAH) is a major cause of subsequent morbidity and mortality. Cilostazol, a selective inhibitor of phosphodiesterase 3 (PDE3), may attenuate cerebral vasospasm because of its antiplatelet and vasodilatory effects. A multicenter prospective randomized trial was conducted to investigate the effect of cilostazol on cerebral vasospasm.

Materials and Methods

Inclusion criteria

- SAH caused by ruptured anterior circulation aneurysm
- H&K grades I to IV
- treated by clipping

Randomization and treatment protocol

- Patients were randomly allocated to the usual therapy group (control group) or the add-on cilostazol 100mg twice daily for 2 weeks group (cilostazol group).
- Nimodipine, a calcium channel blocker indicated to reduce poor outcome related to aneurysmal SAH, was not administered because it has not been approved yet in Japan.

Primary endpoint

- The onset of symptomatic vasospasm (SVS)

Secondary endpoints

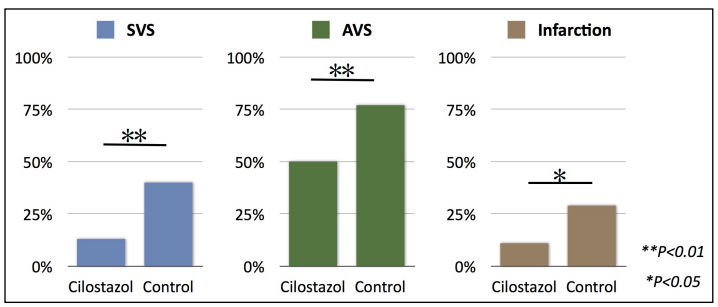
- The onset of angiographic vasospasm (AVS)
- AVS (-) ; <25% decreases / AVS (+); >25% decreases
- New cerebral infarctions related with cerebral vasospasm
- Clinical outcome (modified Rankin scale 0-2 or 3-6)
- Length of hospitalization

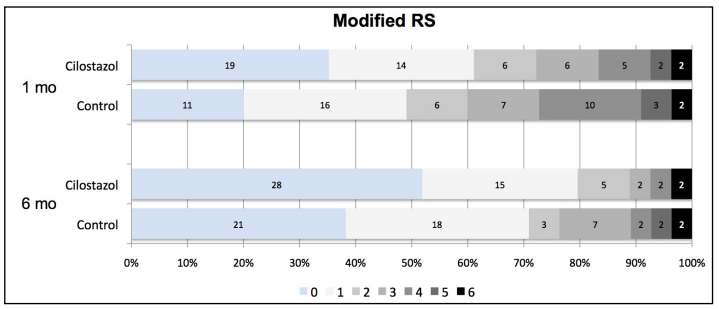
(University Hospital Medical Information Network Clinical Trials Registry, number UMIN000004347)

Results

From November 2009 to December 2010, 109 patients were allocated to the cilostazol group (n= 54) or the control groups (n= 55). No difference was found between the patient characteristics between these groups.

The incidence of SVS, AVS and new cerebral infarctions was significantly lower in the cilostazol group than the control group.





Clinical outcomes at 1 and 6 months after SAH of the cilostazol group was better than that of the control group, although significant difference was not shown.

There was also no significant difference in the length of hospitalization between the groups. No severe adverse event occurred during the study period.

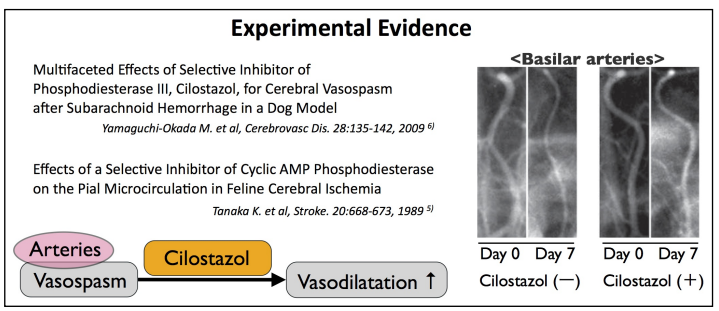
Summary of Results

- Cilostazol effectively reduced the incidence of SVS and AVS.
- Cilostazol reduced the incidence of new cerebral infarctions.
- Cilostazol tended to improve the clinical outcome although no significant difference was shown.

Discussion

Mechanism of cilostazol effect for cerebral vasospasm

Cilostazol is a platelet aggregation inhibitor used for the treatment of symptomatic intermittent claudication associated with peripheral arterial disease or for the prevention of recurrent cerebral infarction except that caused by cardiogenic embolism. Cilostazol does not increase occurrence of cerebral hemorrhage1),4) and selectively inhibits PDE3 resulting in increase of intracellular cyclic adenosine monophosphate.2) PDE3 is an isoform strongly expressed in platelets and vascular smooth muscle cells (SMCs), so the effects of cilostazol are basically mediated by inhibition of PDE3 in SMCs and platelets, leading to relaxation of intact SMCs and inhibition of platelet aggregation. The present findings that the incidence of SVS, AVS and new cerebral infarctions were significantly lower in the cilostazol group may be supported by these reports.



Reason for no difference in clinical outcome between groups

The clinical outcome is possibly affected by not only cerebral vasospasm but also by other factors, such as initial brain damage, surgical complications, or systemic complications. Therefore, a larger number of patients are required to prove the significant effects of cilostazol administration on clinical outcome.

Limitations

Given the risk of recurrent subarachnoid hemorrhage,3) most patients with SAH caused by ruptured anterior circulation aneurysm had been treated by clipping rather than endovascular treatment in all participating neurosurgical institutes before the start of this study. The enrollment was limited to patients with SAH caused by ruptured anterior circulation aneurysm treated by clipping to avoid bias of treatment modality. Today, the number of endovascular treatment for ruptured anterior circulation aneurysm has been increased in all participating neurosurgical institutes as well as in the world. Therefore, additional evaluation for cases treated by coiling is necessary for general versatility.

This study demonstrated that cilostazol may be safe for the acute stage of SAH and effective for the prevention of cerebral vasospasm and for improvement of final outcome after surgical treatment for aneurysmal SAH. These preliminary findings need to be further explored by prospective randomized double-blind trials with placebo.

Conclusion

Oral administration of cilostazol is simple and effective to prevent cerebral vasospasm with a low risk of severe adverse events.

References

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