The Role of Cilostazol for the Tx of SVD

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Submission date: 02-Jun-2020 06:53PM (UTC+0700)
Submission ID: 1336473328
File name: artikel_c37.pdf (100.69K)
Word count: 1080
Character count: 6224

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Key Message

Cerebral Small Vessel Disease(cSVD) is a spectrum of clinical and imaging abnormalities linked to the pathology of small penetrating arteries and arterioles in the brain irrigating subcortical structures. cSVD is the most prevalent neurological disorder in the aging society of the developed world. The prevalence of its seemingly asymptomatic manifestations -silent brain infarcts- increases with age from approximately 6-7% at 60 years to 28% at 80 years of age. Thus, improved management of cSVD based on better understanding of the disease is of great importance. Although there are no specific treatment for strokes caused by cSVD, the Cilostazol Stroke Prevention Study(CSPS) suggested that cilostazol has a specific effect against cSVD. For general stroke prevention (not specific to Small Vessel Infarcts), CSPS-11 study demonstrated the noninferiority of cilostazol to aspirin

Cerebral Small Vessel Disease

cSVD is a spectrum of clinical and imaging abnormalities linked to the pathology of small penetrating arteries and arterioles in the brain irrigating subcortical structures. cSVD is the most prevalent neurological disorder in the aging society of the developed world. The prevalence of its seemingly asymptomatic manifestations- silent brain infarcts- increases with age from approximately 6-7% at 60 years to 28% at 80 years of age.

In another study, lacunar infarcts were found in 23% of all subjects *over* 65 years, and in 43% of subjects *over* 80 years of age. Thus, improved management of cSVD based on better understanding of the disease is of great importance.

Definition of Cerebral Small Vessel Disease

The term cSVD encompasses all the pathological processes that affect the small vessels of the brain, including small arteries and arterioles but also capillaries and small veins. Unlike large vessels, small vessels cannot be currently visualized in *vivo;* therefore, the parenchyma lesions that are thought to be caused by these vessel changes have been adopted as the marker of small vessel disease , and small vessel disease has become a synonym of brain parenchyma lesions.

Pathogenesis of Cerebral Small Vessel Disease

cSVD has two principal forms. One is cSVD of the long perforating arteries irrigating the deep white matter areas mainly in the centrum semiovale that leads to ischemic white matter changes(WMC) and small, often silent lacunes. And the other form is cSVD that affects the deep perforating arteries irrigating the deep gray and white matter in the internal capsule, the basal ganglia, the brainstem, and the cerebellum, which together have been entitled the vascular centrencephalon.

The etiology of cSVD is heterogeneous, probably multifactorial and not completely known. cSVD of the long perforators seems to be mainly caused by arteriolosclerosis and lipohyalinosis, whereas cSVD of the deep perforators appears mainly atherosclerotic. The vessel changes in cSVD include obliteration, occlusion, elongation and tortuosity. Further vessel influence in cSVD relates to endothelial dysfunction, including blood-brain barrier and carrier change, extravasation of plasma proteins and perivascular changes.

One feature of cSVD is decreased vascular density and, for example, cholinergic deafferentation of the small vessels. Phenotypic modulation of smooth muscle cells in the small vessels, from contractile to synthetic phenotype, has also been suggested as a mechanism behind cSVD, leading to changes in the neuropil including microglial activation, loss of oligodendrocytes, and demyelination. Other factors related to cSVD are oxidative stress, inflammatory factors and apoptosis. In addition of importance are systemic vascular, cardiac and carotic hemodynamic changes, as well as decreased venous drainage related to, for instance, venous collagenosis, obstructive sleep apnea and chronic obstructive pulmonary disease (COPD).

Clinical Presentation

cSVD presents clinically either as lacunar stroke with an acute and focal neurological deficit, or as more diffuse conditions such as gait instability, urinary incontinence, progressive cognitive decline and dementia, and mood disorders. The four main clinical lacunar stroke syndromes are pure motor stroke, pure sensory stroke, sensorimotor stroke, and ataxic hemiparesis, followed by some other less common syndromes. A subcortical location is the common factor for the neuroradiological features of cSVD, which are either ischemic changes, bleeds or venous changes. Ischemic changes include WMC, lacune, enlarged perivascular changes and cortical microinfarcts. Bleeds include aneurysmatic bleeds, lobar hemorrhages and microscopic bleeds.Venous changes such as venous collagenosis involve, for example, deep galenic veins but these changes are less well characterized than arterial changes.

The Role of Cilostazol

The use of antiplatelet drugs such as aspirin, aspirin plus dipyridamole and ticlopidine has shown equal efficiency in secondary stroke prevention after a stroke caused by cSVD. In one clinical trial, cilostazol, an antithrombotic and vasodilating drug, reduced the risk of recurrent stroke especially in patients with lacunar infarction, suggesting that cilostazol could have a specific effect against cSVD.

Cilostazol is an antiplatelet agent that inhibits (like dipyridamole) PDE in platelets and vascular endothelium. (Figure 1) However, cilostazol inhibits type 3 PDE, which is specific for cyclic adenosine monophosphate. Cilostazol is known to have both antiplatelet and a vasodilating effect as an essential effect of PDE inhibitors. It is being used as a general anti-thrombotic agent and in the stroke prevention in some Asian countries. In the US and EU, Cilostazol is approved for the "Intermittent Claudication".

Cilostazol Stroke Prevention Study

The CSPS was a multicenter, randomized, placebo-controlled, double-blindclinical trial examining the effects of cilostazol on the recurrence of cerebral infarction.

Cilostazol is an antiplatelet agent that increases the cyclic adenosine monophosphate levels in platelets via inhibition of phosphodiesterase . Cilostazol was found to reduce the risk of secondary stroke by 41.7% compared with placebo. CSPS investigators reported that the greatest risk reduction was found in patients who initially had a "lacunar" infarction (43.4% in cilostazol versus placebo, P = 0.0373), suggesting that cilostazol has a specific effect against cSVD. (Figure2) These clinical benefits were not associated with adverse events. The clinical implications of the CSPS results are limited due to the fact that patients were also not randomized to the aspirin (ASA:a standard antiplatelet treatment at the time of the study). Thus, direct comparison of the cilostazol and ASA effect was not made.

In conclusion, cSVD is the most prevalent neurological disorder in the ageing society of the developed world and the cause of about a quarter of all acute ischemic strokes. Although there are no specific treatment for strokes caused by cSVD, the CSPS suggesting that cilostazol has a specific effect against cSVD. For general stroke prevention (not specific to Small Vessel Infarcts), CSPS-11 study demonstrated the noninferiority of cilostazol to aspirin.

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