

## Efficacy of Cilostazol + Nimodipine on Cerebral Vasospasm Following Aneurysmal Subarachnoid Hemorrhage

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### Abstract

**Introduction:** Cerebral Vasospasm (VSP) accounts for 39% of morbidity following aneurysmal Subarachnoid Hemorrhage (SAH), occurring between days 4 and 14, with mean time of onset of 7.7 days after the ictus. Nimodipine has shown to prevent cerebral VSP after SAH.

**Objective:** This clinical trial aimed to determine the efficacy of oral nimodipine and cilostazol combination in preventing vasospasm following aneurysmal SAH.

**Methodology:** This is a prospective, randomized, open-label, blinded end point study to establish whether the combination of nimodipine and cilostazol will reduce the incidence of VSP arising from spontaneous aneurysmal SAH. The primary endpoint is the onset of cerebral VSP as manifested by increasing trend of Lindergaard Index (LI) during Transcranial Doppler (TCD) monitoring. A total of 144 patients were recruited from May 2014 to December 2015 and randomized to 2 groups. Group A (control) received nimodipine 60mg every 4 hours for 21 days. Group B (treatment) received nimodipine 60mg every 4 hours for 21 days, and cilostazol 100mg every 12 for 14 days. Transcranial Doppler (TCD) monitoring was done daily for measurement of LI.

**Conclusion:** The combination of oral nimodipine 60 mg every 4 hours for 21 days and cilostazol 100 mg every 12 hours for 14 days is well tolerated and reduced the incidence of vasospasm following aneurysmal SAH compared to nimodipine alone.

### Introduction

Aneurysmal Subarachnoid Hemorrhage (SAH) accounts for only 2%-5% of all strokes but carries a high mortality of 22%-25% of deaths secondary to cerebrovascular diseases [1]. For patients who survive, a high morbidity has been recorded secondary to its complications such as rebleeding, hydrocephalus, seizures and cerebral vasospasm.

Cerebral Vasospasm (VSP) accounts for 39% of morbidity following aneurysmal SAH [2], occurring between days 4 and 14, with mean time of onset of 7.7 days after the ictus [3]. Following a well-utilized scoring system, the Fisher grading determines the degree of subarachnoid blood and the risk of VSP [4]. Detection of the onset of VSP with high confidence after aneurysmal SAH is important. The Digital Subtraction Angiography (DSA) and

the Transcranial Doppler (TCD) are the two most commonly employed procedures. DSA is the gold standard imaging modality [5,6], with nearly 100% sensitivity and specificity for detection of VSP. However, its use has been limited by its relative invasiveness, high cost, along with the tedious time-consuming performance of serial studies.

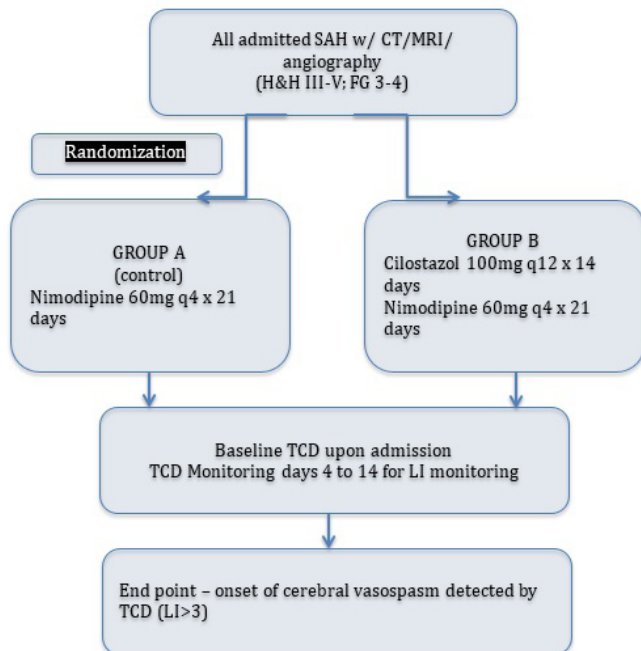
On the other hand, TCD is a noninvasive, and safe tool that is also widely used for detection of VSP. It is highly specific (89%-98%) and sensitive (84%-93%) [7] and may be used daily with minimal cost and risk to patients. Aside from absolute increase in mean flow velocity, determining the LI, is an important information to support the presence of VSP [1,3]. Numerous studies have been published regarding the medical management on the prevention of VSP after aneurysmal SAH. The use of calcium channel

blocker, nimodipine, has been widely used to prevent the onset of cerebral vasospasm and has been part of the standard treatment to prevent the onset of VSP. It reduces the relative incidence of cerebral infarction secondary to cerebral vasospasm as a result of subarachnoid hemorrhages by 34%, and poor outcome by 40% [8]. Cilostazol on the other hand has been shown to prevent VSP in some studies [2]. It selectively inhibits phosphodiesterase (PDE)-3 found in platelets and vascular smooth muscle cells, resulting in its vasodilatory effects [2,9]. It has also significantly improved the functionality of patients upon discharge as evidenced by lower modified Rankin Scale score (mRS) [10].

This clinical trial was conducted to determine if the addition of oral cilostazol to oral nimodipine would further reduce the risk of VSP. Specifically, this aimed to prove that the combination of nimodipine and cilostazol would prevent the occurrence of cerebral vasospasm by 50% as compared to nimodipine alone (34%).

## Methodology

Consecutive patients admitted due to aneurysmal SAH during the first 96 hours after onset and confirmed by cranial Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) were included in this study. Specifically, patients with Hunt and Hess III-IV and Fisher Grade 3-4 were included since higher scores posed greater risk of developing VSP. Aneurysms confirmed by angiography located in the anterior circulation were recruited (Figure 1).



**Figure 1:** Flow chart of the selection and randomization of subjects.

SAH secondary to other causes like ruptured arteriovenous malformation or trauma; pregnancy; pre-existing renal, hepatic, cardiac or pulmonary disease; rebleeding or re-rupture; relatives unwilling to give consent; poor acoustic window; and patient with poor compliance to medications defined by more than 1/3 missed daily doses were excluded. Additionally, patients with VSP prior to initiation of the medication/s were also excluded. A written informed consent was obtained from the patients or their relatives of nearest kin. The Institution's Review Board and Ethics committee approved the study.

The sample size was calculated as follows: following the reduction rate of VSP with the use of nimodipine by 34%, the addition of cilostazol we hypothesized that it would further reduce this risk by 50%, with 0.5 significance level and 80% power, the computed sample size is 144 for both groups.

Treatment was started during the first 96 hours after the initial onset of SAH, and continued for 21 days. Patients were randomized into two groups. Group A received nimodipine 60 mg every 4h (control group) while Group B received cilostazol 100 mg BID + nimodipine 60 mg every 4h. Nimodipine and cilostazol were administered for 21 and 14 days, respectively. The treatment dose and length of use for the 2 drugs were based on results of previous studies [2,8,11-13].

Baseline TCD and subsequent examinations to determine LI were done upon admission by a technician under the supervision of a physician not aware of treatment allocation. Daily monitoring of LI on days 4 to 14 were performed. An increasing trend in LI (>3) is considered as the onset of VSP.

The rates of vasospasm were determined from both groups and the relative risk reduction for the occurrence of VSP was then calculated. The number needed to treat was determined after calculating for the absolute risk reduction. Moreover any adverse reactions were recorded.

## Results

A total of 144 patients were recruited in the trial from May 2014 to December 2015. Eleven patients were excluded; among these, 7 died during the first 24 hours due to rebleeding; the other 4 had poor acoustic. Among those who had rebleeding, 5 were from nimodipine group, and 2 were from the nimodipine plus cilostazol group.

Table 1 summarizes the baseline characteristics of the two groups which did not show any significant difference, except for presence of diabetes mellitus, which was lower among the nimodipine + cilostazol group. The mean time from ictus to entry was 1.2 days. Twenty-one of the 72 (29.67%) patients in the nimodipine group developed VSP while 11 out of 67 (16.42%) patients had the primary outcome in the nimodipine plus cilostazol group.

	Patients on nimodipine (n=72)	Patients on nimodipine+cilostazol (n= 61)
Age (years)	50.2	58.7
Men	33	36
Women	39	25
Hypertension	55	48
Diabetes mellitus	32	17*
Cardiovascular diseases	56	49
Previous stroke	1	4
Previous SAH	0	0
Systolic BP (mmHg)	186	190
Seizure at ictus	8	3
Loss of consciousness at ictus	49	43
GCS on admission (mean)	10	13
Hunt & Hess score		
1		
2		
3		
4	33	35
5	39	26

Fisher grade		
1		
2		
3	43	39
4	29	22
Time from ictus to CT scan (hrs)	19.8	16
Angiography	41	39
Aneurysm (clinical)	28	22
1. Acom	2	1
2. Pcom		
3. ACA	2	3
4. MCA		
5. PCA	9	12
	0	1
Surgical procedure	9	13
Vasospasm	21	11*
*p value <0.05		

**Table 1:** Demographic data and indices of severity of initial subarachnoid hemorrhage in patients treated with nimodipine or nimodipine+cilostazol.

Cutoff value for LI of >3 was defined as probable vasospasm, while a value of >6 is definite vasospasm. In this study, a value of >3 was used to indicate presence of VSP.

The combination of nimodipine and cilostazol compared to nimodipine alone has shown to have a significant rate of reduction in the occurrence of VSP (RRR-62%). Furthermore, the number needed to treat was calculated as 9. (Table 2).

	Control group (nimodipine) n= 72	Treatment group (nimodipine+cilostazol) n= 61	Relative risk reduction (%)	Confidence interval (95%)	p value
Vasospasm	21 (29)	11(18)	62	26 to 68	0.001

**Table 2:** Effect of nimodipine+cilostazol on incidence of vasospasm following aneurysmal SAH. Values are in percentages of patients.

## Discussion

Cerebral VSP is an important neurologic problem, its pathophysiology is still not well understood [14]. Our study has shown that the addition of cilostazol to nimodipine in the prevention of VSP after spontaneous SAH can further prevent the incidence of VSP compared to nimodipine alone by transcranial Doppler monitoring. Additionally, the safety of the combination has also been established.

Previous studies revealed a synergistic effect of Phosphodiesterase (PDE) inhibitors [15], along with nimodipine,

in preventing VSP. Phosphodiesterase inhibitors were shown to potentiate the action of endogenous Nitric Oxide (NO) released by endothelial cells, leading to smooth muscle relaxation of all intracranial vessels. In one study using the PDE-5 inhibitor tadalafil, it was shown through measurement of vessel wall diameter that this PDE inhibitor has vasodilatory effect on both acute and chronic periods of VSP following SAH [16].

Another PDE inhibitor with vasodilatory and inotropic effect used in clinical trials for treatment of VSP after aneurysmal SAH was milrinone [17]. This PDE-3 inhibitor given as intraarterial infusion up to day 14, in combination with oral nimodipine, can be

effective and safe for VSP treatment. The findings demonstrated a significant enlargement in the diameter of vasospastic intracranial arteries [18].

The use of a selective PDE-3 inhibitor cilostazol given intravenously in combination with oral nimodipine demonstrated significant effect in preventing VSP [15]. These favorable results were due to previously established benefits of cilostazol use including its vasodilatory, antiapoptotic, anti-inflammatory and neuroprotective effects.

On the other hand, nimodipine acts on cerebral arterioles [9], which are also the target of cilostazol resulting to a synergistic vasodilatory effect [2]. Calcium channel blockers have proven benefit but their vasodilating effects on spastic cerebral arteries is relatively modest. Any adverse effects due to a possible interaction of both drugs were monitored but none that is significant were identified. Cilostazol does not prolong bleeding time despite being an antiplatelet [17,19-24]. Likewise, surgical clipping among these patients had unremarkable outcome despite intake of cilostazol.

This study has certain limitations. Ischemia resulting from VSP was not determined in this study utilizing available neuroimaging. We focused on the prevention of VSP utilizing the combination of nimodipine and cilostazol by monitoring with TCD, a noninvasive test rather than cerebral infarction due to VSP.

This study concludes that the combination of oral nimodipine 60 mg every 4 hours for 21 days and cilostazol 100 mg every 12 hours for 14 days, is well tolerated and reduces the incidence of vasospasm following aneurysmal SAH compared to nimodipine alone.

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