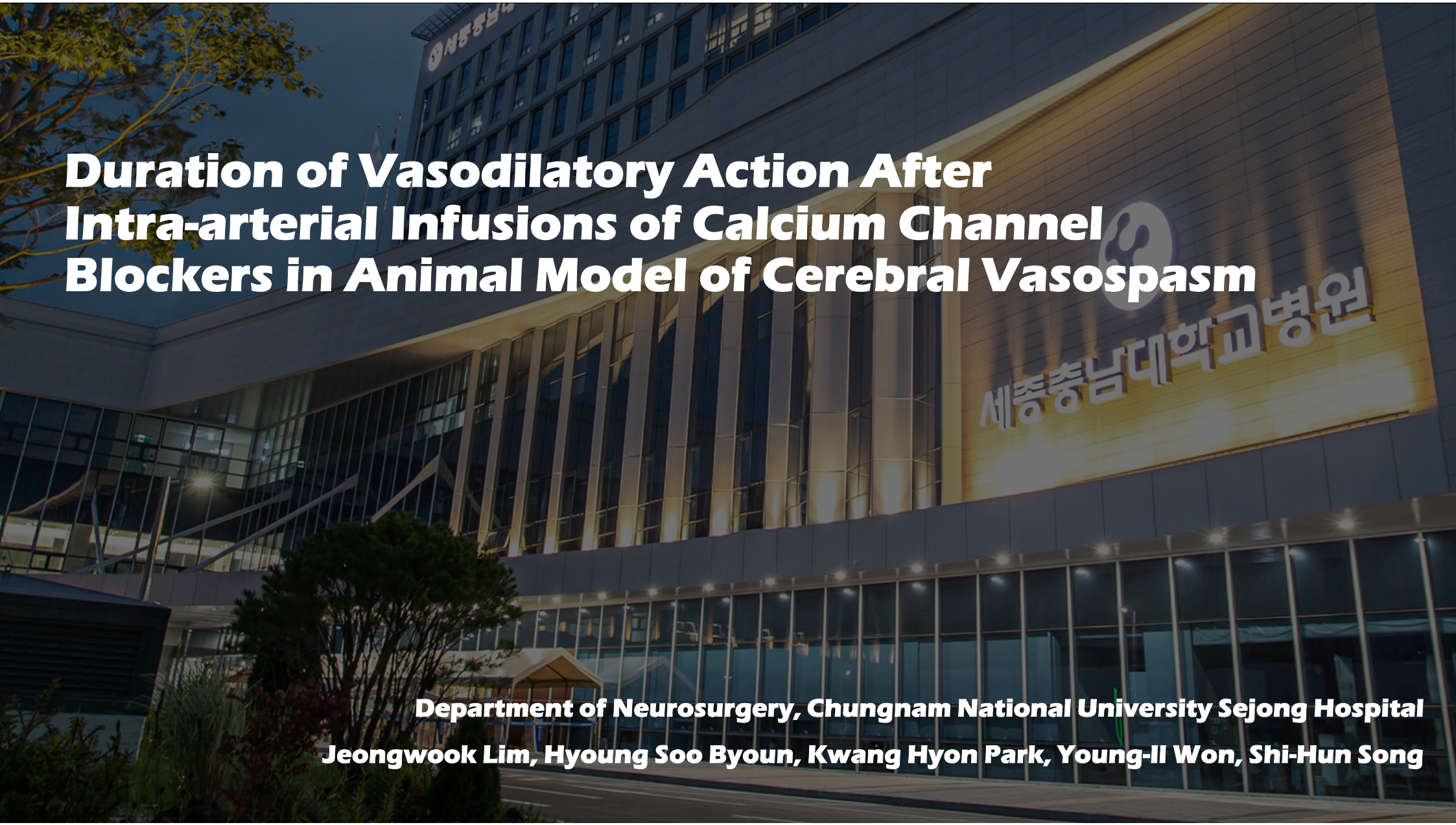

Duration of Vasodilatory Action After Intra-arterial Infusions of Calcium Channel Blockers in Animal Model of Cerebral Vasospasm

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Introduction

- Vasospasm after rupture of cerebral aneurysms is the primary cause of heightened patient morbidity and mortality and is a relatively common complication of SAH seen by angiogram in two-thirds of patients with rupture and one-third of those with clinical symptoms.
- Conservative treatment is a priority in instances of vasospasm, but oral nimodipine is the only agent to date with known benefits. Other interventions, including IA chemoangioplasty, intrathecal drug infusion, balloon angioplasty, or angioplasty by retrievable stent, have also been performed in severely symptomatic patients refractory to medical treatment. However, mechanical angioplasty via balloon and/or retrievable stent has very limited application if proximal arterial segments are involved.
- There are ample studies of chemoangioplasty by IA infusion of drugs, particularly CCBs and phosphodiesterase inhibitors. CCBs are otherwise relatively well known and are frequently used for their positive effects, although seldom directly compared. Moreover, there was no consensus that how long the vasodilatory action of IA chemoangioplasty is maintained and how many times a day should the chemoangioplasty be performed to avoid cerebral ischemia. The present investigation was launched to examine characteristics of the three most popular CCBs used for chemoangioplasty: nicardipine, nimodipine, and verapamil. A rabbit animal model enabled side-by-side comparisons, focusing on duration of the vasodilatory action based on angiography.

Materials and methods (I)

- A total of 36 experimental rabbits weighing 2.5–3.0 kg were used for experiment. Intramuscular injection of ketamine and xylazine was used for anesthesia. After anesthesia, femoral artery was exposed & punctured, then a 4-Fr introducer was installed, blood pressure were achieved through transducer. Once cerebral angiography was completed, the introducer was positioned within subcutaneous space for later follow-up angiography. Three days after inducing SAH of the brain, angiography was again conducted, expedited by the introducer still in place. SAH was induced by obtained autologous arterial blood through introducer, and SAH was identified by the fluoroscopy and CT (Fig A & B).
- Both 17 microcatheters and 0.14 microwires were engaged for cerebral angiography and IA drug infusion. Prior to induction of SAH, cerebral angiography was routinely performed to determine vertebral and basilar arterial calibers at baseline for later referencing. On Day 3 of the SAH animal model, angiography was repeated to verify vasospasm of basilar artery, defined as > 30% luminal compromise relative to baseline status. Any animals with < 30% arterial narrowing were ineligible for further participation.
- Rabbits showing acceptable vasospasm were randomly assigned to IA drug infusion as follows: group C, nicardipine (0.06 mg/kg); group M, nimodipine (0.05 mg/kg); or V group, verapamil (0.1 mg/kg). If blood pressure fell by 20% (relative to baseline), infusion was reduced by 50%. Infusion was stopped if blood pressure decline continued. After administration, initial drug efficacies were assessed by comparing degrees of vasospastic easing at points of severest luminal compromise (see Fig. 2b). Follow up angiography was performed hourly for 5 h after IA infusion, measuring luminal calibers (Fig. 2c) to confirm that original vasospastic states had returned.
- Arterial diameters were determined via single-blind computer application for cerebral angiography. Luminal spasms were graded, based on percentage of baseline arterial diameter lost, whereas vasodilative effects after IA infusion represented percentages of vasospastic reversal.
- For group-wise analyses of vasodilative effects and blood pressure change after IA infusion, the Wilcoxon signed-rank test was used. The Kruskal–Wallis test was applied to group comparisons of vasodilatory degree, duration of action, and blood pressure change after IA infusion. If statistically significant, the Bonferroni correction for multiple comparisons was invoked. All computations were driven by standard software (SPSS v21.0) setting significance at $p < 0.05$.

Materials and methods (II)

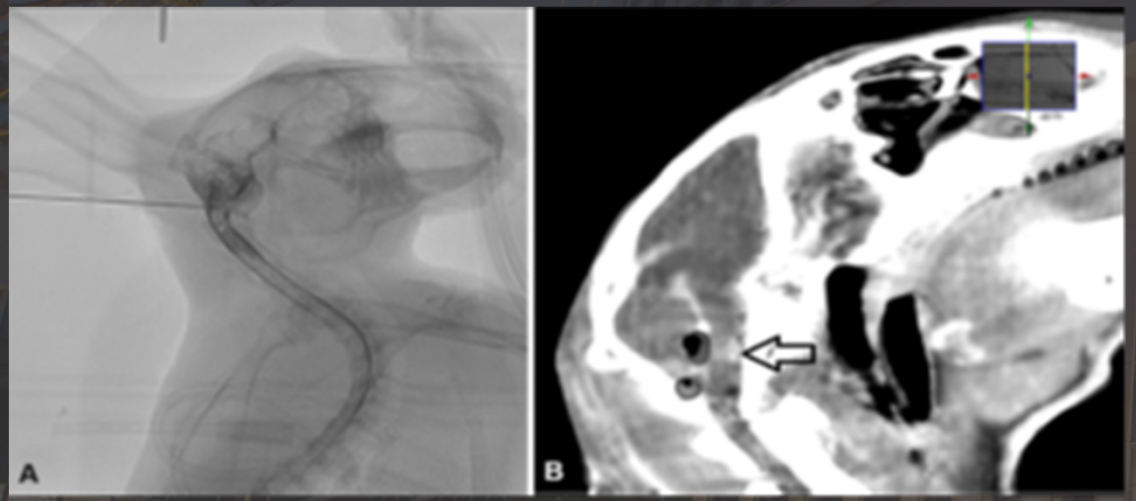

Fig. 1 Induction and confirmation of cerebral subarachnoid hemorrhage (SAH): A, cisternography of rabbit through occipito-atlantal membrane and B, sagittal reconstruction of computed tomography brain image in rabbit (black arrow denoting SAH and intraventricular hemorrhage)

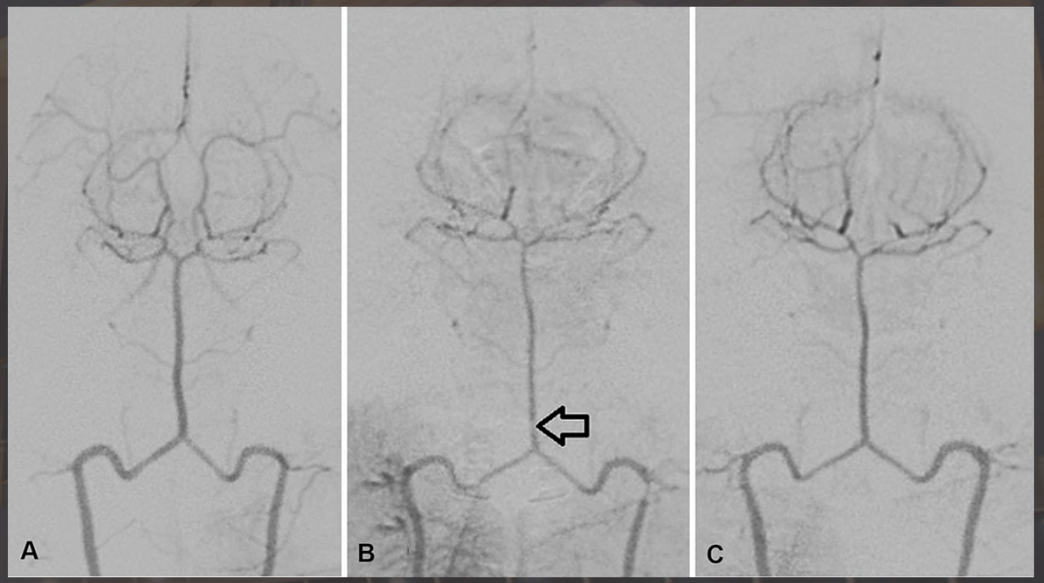

Fig. 2 Digital subtraction angiogram of vertebrobasilar artery in rabbit: A, Angiographic image prior to hemorrhage; B, Follow-up angiographic image 3 days after subarachnoid hemorrhage (black arrow at most severe point of vasospasm); and C, angiographic image immediately after IA drug infusion

Results

➢ Efficacy of intra-arterial CCBs Infusion

Table 1. Changes in basilar artery diameter after calcium channel blockers administration and comparison of the diameter of the residual basilar artery between groups.

Group / Hour	C-group (n=7)		N-group (n=8)		V-group (n=7)		Comparison of the diameter between groups	
	Diameter (%)* (Min, Max)	p-value	Diameter (%)* (Min, Max)	p-value	Diameter (%)* (Min, Max)	p-value	p-value‡ (Cross-group comparison) §	
Spasm	63(45, 68)		59(45, 69)		62(47, 63)			
IADI	80(51, 90)	0.017†	75(73, 100)	0.012†	72(62, 85)	0.018†	0.466	
1 hour	89(75, 93)	0.018†	80(73, 100)	0.012†	57(49, 63)	0.799	0.003‡	V&N = 0.008 §
								V&C = 0.002 §
								N&C = 1.00
2 hours	81(36, 84)	0.046†	72.5(52, 86)	0.051	53(46, 61)	0.206	0.017‡	V&C = 0.022 §
								V&N = 0.082
								N&C = 1.000
3 hours	67(36, 84)	0.176	67(45, 77)	0.249	51(44, 66)	0.248	0.61	
4 hours	63(37, 79)	0.357	59(44, 87)	0.624	51(46, 60)	0.093	0.105	
5 hours	65(39, 78)	0.462	65.5(45, 81)	0.779	54(44, 60)	0.310	0.379	

C group: nicardipine group, M group: nimodipine group, V group: verapamil group, *The median diameter of basilar artery before and after intra-arterial drug infusion at each time, IADI immediately after intra-arterial drug infusion, Min minimal value,Max maximal value

† $p < 0.05$ versus diameter of basilar artery before drug administration. ‡p value < 0.05 versus each group

§ Level of significance was adjusted with Bonferroni correction for multiple comparisons

➢ Change in Mean Arterial Pressure During and After IA Infusion

- Blood pressure changes during and after IA infusion were observed in C group, the average arterial pressure falling by 10 mmHg within 1 h after IA infusion. However, there was gradual recovery after 2 h, with normalization of blood pressure after 3 h. Almost no change in blood pressure was observed in groups M and V groups after IA infusion

Discussion

- In the present study, all CCBs exerted vasodilatory effects immediately after IA infusions, but they did not differ overall in degrees of vascular relaxation ($p = 0.466$). Verapamil recipients showed maximum effects immediately after infusion, whereas the other agents (groups C and M) peaked 1 h after infusion. They also proved more potent than verapamil, falling short of significance ($p = 0.193$). The vasodilatory effects observed in groups C and M were sustained for 2 h, as opposed to < 1 h in group V, corresponding with respective drug half-lives (8-9 h for nimodipine and nicardipine; 3-7 h for verapamil). In our study, the vasodilatory effects achieved by IA infusion using CCB were not sustained beyond 2 h in any of the CCB groups, and it may be a limitation of IA chemoangioplasty in vasospasm. Due to poor durability of the chemoangioplasty, repeated procedure may be required in severe vasospasm. Moreover, there has been no standard for how many procedures a day should be performed in order to relieve radiologic vasospasm or to stabilize clinical symptoms. And nicardipine triggered systemic hypotension during and after IA infusion, unlike the other CCBs. It may be thus inferior in maintaining cerebral perfusion.
- In the class of benzothiazepines, verapamil (amphiphilic nature) reacts selectively with myocardium and is useful for coronary vasospasm. The reason for its utility in the brain is that both coronary and cerebral arteries are structurally similar, and both are subject to vasospasm. On the other hand, each differs distinctly in the nature of vasospasm, which may be transient in coronary arteries but prolonged cerebral arteries, lasting for 2 weeks. Despite various reports of its usage for cerebral vasospasm, verapamil has a short half-life compared with other drugs and may be better suited for treating coronary vasospasm.
- It has not been well known about the equivalent dosage of each CCB drug. However, the dose of each drug used in our study was greater than the maximum vasodilatory dose in the dose–response curve of other studies. Therefore, we judged that the maximum relaxation effects of each CCB could be compared with each other.

Conclusion

- After IA infusion for vasospasm, all CCBs tested produced effective vasodilation based on angiography. Compared with verapamil, nimodipine and nicardipine exhibited longer durations of action, but only the nicardipine group displayed systemic hypotension during and after infusion. Unfortunately, the vasodilatory effects achieved by IA chemoangioplasty were not sustained for > 2 h in any of the treatment groups. Therefore, the new alternative should be found and verified to extend the duration of vasodilatory action in severe vasospasm, besides IA infusions of CCBs.

- Disclosure

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: Conflicts of interest : The authors declare no conflict of interest.

: This study was approved by the Committee for Ethical Animal Experimentation at our institution and was in compliance with all recommendations made.