Furthermore, clopidogrel resistance were thought to enhance major cardiovascular events and death may in patients with acute myocardial infarction and patients who treated with coronary stent. Therefore, we evaluated the prevalence and risk factors of clopidogrel resistance, and association between thromboembolic complications and clopidogrel resistance in patient with stent-assisted angioplasty for atherosclerotic cerebrovascular disease.

**MATERIALS AND METHODS**

Between September 2006 and June 2008, clopidogrel resistance test was performed on 43 patients who underwent stent-assisted angioplasty for atherosclerotic cerebrovascular disease. Two patients were excluded. We did not check clopidogrel resistance test in 2 patients. Clopidogrel resistance test was performed before drug administration and about 12 hours after drug administration (loading dose : 300 mg, maintain dose : 75 mg).

**INTRODUCTION**

Peri-procedural administration of aspirin and clopidogrel are considered as "standard of care" to prevent perioperative thromboembolic complications. Clopidogrel is an ADP-receptor antagonist. After oxidized by hepatic cytochrome P450, selectively and irreversibly blocking the P2Y12 receptor and then causes an irreversible blockade of ADP binding. But, recently, approximately 15% to 30% of patients have been reported to be resistant to clopidogrel. Also, prevalence of clopidogrel resistance has been reported from 42.9% to 62.3% those patients who underwent cerebrovascular stent placement procedure. Furthermore, clopidogrel resistance were thought to enhance major cardiovascular events and death may in patients with acute myocardial infarction and patients who treated with coronary stent. Therefore, we evaluated the prevalence and risk factors of clopidogrel resistance, and association between thromboembolic complications and clopidogrel resistance in patient with stent-assisted angioplasty for atherosclerotic cerebrovascular disease.
Among 41 patients, 18 patients had intracranial lesions, and 23 patients had extracranial lesions. We used the VerifyNow-p2Y12 rapid analyzer (Accumetrics, San Diego, CA, USA) to measure platelet inhibition rate. We defined clopidogrel resistance as percentage platelet inhibition <20%.

We analysed our data by using commercial software (SPSS version 14.0, SPSS Inc., Chicago, IL, USA). We used independent t-test, uni-variate (Fisher’s exact test) and multi-variate (binary logistic regression) analysis to evaluate associations between variable predictive factors and clopidogrel resistance. We used Mann-Whitney U test to evaluate the relationship between thromboembolic event and clopidogrel resistance. p<0.05 was considered statistically significant.

### Endovascular procedures

Endovascular procedures were performed under local anesthesia. Arterial access was achieved via the femoral artery. A guiding catheter was placed in the internal carotid artery. We used 6F; 7F; 8F guiding catheter system (Envoy; Cordis, Bridgewater, NJ, USA), through the femoral artery via the vascular sheath. Cerebral angiography was done by using these guiding catheters with heparin infusion (heparin 5,000 IU mix normal saline 1,000 mL) during intervention. Then, a microcatheter (Echelon-10; ev3, Irvine, CA, USA) was advanced and placed into the stenotic lesion using (x-pedion 0.014-inch microwires, ev3, Irvine, CA, USA) via conventional technique.

Stent insertion was carried out using the following stents : Wallstent (Boston Scientific, Natick, MA, USA), and Cypher (Cordis, Bridgewater, NJ, USA)

### RESULTS

Among 41 patients, 25 patients were male and 16 patients were female. Mean age was 67.59±7.10 years (range : 41-79). Intracranial lesions were 18 (43.9%) cases, and extracranial lesions were 23 cases (56.1%). Overall clopidogrel resistance was 23.73±28.60 (range : 0-96). Twenty-two patients showed clopidogrel resistance (4.86±5.83%). Prevalence of the clopidogrel resistance in patients who underwent stent-assisted angioplasty was 53.7%.

Clinical comparison between clopidogrel resistant group (CRG) and clopidogrel sensitive group (CSG) was demonstrated in Table 1. Base, P2Y12 reaction unit before drug administration, was 267.82±62.53 in CRG and 249±72.56 in CSG (p=0.378). PRU, P2Y12 reaction unit after drug administration, was 279.05±54.42 in CRG and 120.74±65.29 in CSG (p=0.00001). Platelet aggregation inhibition was markedly decreased in CRG. PRU showed decreased platelet aggregation inhibition in CRG. Platelet inhibition rate was 4.86±5.83 in CRG and 53.42±21.05 in CRG (p=0.00001).

In this study, we found hypercholesterolemia was a statistically significant risk factor associated with clopidogrel resistance by using univariate and multivariate analysis (p=0.036 and p=0.037, respectively) (Table 2).

We analysed association between the incidence of intra-procedural in-stent thrombosis and clopidogrel resistance. Stent-assisted angioplasty was technically successful in all patients, but acute in-stent thrombosis occurred in 5 patients with intracranial lesions (four patients with clopidogrel resistance and one patient without clopidogrel resistance). Acute thrombi were completely lysed after intra-arterial infusion of abciximab. In-stent thrombosis occurred more frequently in CRG than CSG (Table 3).
There were no statistically significant differences in level of WBC, initial platelet count, and CRP (Table 1). Hypertension, diabetes, smoking, previous coronary artery disease history, and previous stroke history showed no significant correlation with clopidogrel resistance (Table 2).

**DISCUSSION**

Recently, older than 55 years-old, diabetes, hypercholesterolemia and greater body weight were reported as predictive factors of clopidogrel resistance in patients who underwent stent-assisted angioplasty. Hypertension and diabetes were more frequent in CRG than CSG (p=0.921, p=0.455, respectively, multi-variate analysis). Older than 55 years-old was not independently significant in this study (p=0.718 and p=0.427, respectively, uni- and multi-variate analysis).

In our study, only hypercholesterolemia was an independent risk factor of clopidogrel resistance (p=0.036 and p=0.037, respectively, uni- and multi-variate analysis). Influence of hypercholesterolemia on clopidogrel resistance is unclear. In a report, the lipophilic statin atorvastatin significantly reduced clopidogrel-induced inhibition of platelet aggregation in a dose-dependent manner at 24h. Both lipophilic statins and clopidogrel are metabolized by hepatic cytochrome P450 isoenzyme. Since Lau et al. many investigators have studied the relationship, but the interaction between statins and clopidogrel is still controversial.

We observed a relation between clopidogrel resistance and in-stent thrombosis. In our study, within 41 patients, 5 patients suffered from in-stent thrombosis (12.2%). Platelet inhibition rate of the four patients were under cutoff value (<20%). After intra-arterial infusion of abciximab 20 mg, thrombi were completely resolved, and there were no neurologic complications (Fig. 1). A comparative photographs of one patient without in-stent thrombosis were demonstrated in Fig. 2. Remarkably, all the 5 patients who suffered from in-stent thrombosis had intracranial lesions. In intracranial lesion group, rate of in-stent thrombosis occurrence was 27.8% in this study. In details, complication rate of intracranial lesion was 40% (4/10) in CRG and 12.5% (1/8) in CSG. It seemed to have a relationship between intracranial lesions and in-stent thrombosis in patients with clopidogrel resistance. Vascular diameter and blood flow might be concerned. But, too small sample size to verify the relation in this study. Lee et al. re-

| Complication | Clopidogrel resistant level mean±SD | Mann-Whitney U test p-value |
|--------------|----------------------------------|-----------------------------|
| +            | 16.2±15.55                       | 0.802                       |
| -            | 28.92±28.02                      |                             |

**Table 3.** Analysys of the accocitation between complication occurrence and clopidogrel resistance

![Fig. 1.](image1.png)  
**Fig. 1.** Angiograms of 59-year-old female. Left M1 distal segment 95% stenosis. Intra-procedural thrombosis is observed. Inhibition rate was 9%. A : Lt M1 stenosis. B : Post-stent insertion. C : Fifteen minutes after stent insertion. D : After Reopro 20 mg Intra-arterial injection. Arrow : Acute thrombus.

![Fig. 2.](image2.png)  
**Fig. 2.** Angiograms of 70-year-old female. Left internal carotid artery (ICA) bifurcation shows severe (99%) stenosis. No intra-procedural thrombosis is observed. Inhibition rate was 38%. A : Lt ICA bifurcation stenosis. B : Post-stent insertion. C : Fifteen minutes after stent insertion.
ported 3 cases of intraprocedural complication. Overall complication rate was 3.1%. All complicated patients belonged to CRG. In clopidogrel repose group, rate of intraprocedural complication was 7.1%. They reported there were no clinical consequences after prompt administration of parenteral abciximab. Ryu et al.\(^2\), reported 5 cases of thromboembolic complication after neurointerventional procedures. These cases showed resistance to both aspirin and clopidogrel. Total thromboembolic complication rate was 9.4%. In their study, 10 patients displayed resistance to both aspirin and clopidogrel. In both resistance groups, thromboembolic complication rate was 50%. This complication rate was relatively high. Platelet inhibition rate of one patient who suffered from in-stent thrombosis in clopidogrel sensitive group in our study was 43%. Lee et al.\(^2\) and Ryu et al.\(^2\) defined clopidogrel resistance as percentage platelet inhibition less than 40%. Although no statistical significance was found in our study, these data suggested that patients who had low platelet inhibition rate were more likely to suffer from peri-procedural thromboembolic complications.

To overcome clopidogrel resistance, several methods are suggested. First, increasing the loading dose and maintenance dose of clopidogrel\(^2\)\(^\text{3}\)\(^\text{4}\). Second, use of the new drugs, whole replacement or addition, such as Prasugrel (CS-747), a novel thienopyridine that inhibits adenosine diphosphate-induced platelet aggregation more rapidly with less intraindividual variability and to a greater magnitude than do standard and higher doses of clopidogrel\(^1\)\(^\text{2}\)\(^\text{3}\)\(^\text{4}\), Ticagrelor (AZD6140), the first reversibly binding oral, direct-acting P2Y12 receptor antagonist\(^1\)\(^\text{2}\)\(^\text{3}\)\(^\text{4}\),\(^\text{5}\)\(^\text{6}\),\(^\text{7}\)\(^\text{8}\),\(^\text{9}\)\(^\text{10}\),\(^\text{11}\)\(^\text{12}\),\(^\text{13}\)\(^\text{14}\),\(^\text{15}\)\(^\text{16}\),\(^\text{17}\)\(^\text{18}\),\(^\text{19}\)\(^\text{20}\),\(^\text{21}\)\(^\text{22}\),\(^\text{23}\)\(^\text{24}\),\(^\text{25}\)\(^\text{26}\),\(^\text{27}\)\(^\text{28}\),\(^\text{29}\)\(^\text{30}\) Cangrelor (AR-C69931) short-acting, IV, reversible inhibitor of P2Y12 receptor\(^2\)\(^\text{3}\)\(^\text{4}\), and Cilostazol, a phosphodiesterase 3 inhibitor.\(^1\)\(^\text{2}\)\(^\text{3}\)\(^\text{4}\),\(^\text{13}\)\(^\text{12}\)\(^\text{13}\)\(^\text{23}\)\(^\text{2}\)\(^\text{3}\)\(^\text{5}\)\(^\text{6}\)\(^\text{7}\)\(^\text{8}\)\(^\text{9}\)\(^\text{10}\) St. John’s Wort, a potent CYP2C19 and CYP3A4 inducer, and a popular herbal remedy used for the treatment of depression, anxiety, and insomnia\(^3\)\(^\text{4}\). We have to observe the clinical results of these drugs to find “standard of care” for the patients shows clopidogrel resistance.

Smoking was not an independent factor influencing clopidogrel resistance in this study, although more frequently seen in PSG (31.8% in PRG, 57.8% in PSG, \(p=0.122\) and \(p=0.168\), respectively, uni- and multi-variate analysis). Some reports suggested a strong relationship between smoking and clopidogrel resistance, known as “Smokog’s Paradox”\(^1\)\(^\text{2}\)\(^\text{3}\)\(^\text{4}\)\(^\text{5}\)\(^\text{6}\)\(^\text{7}\)\(^\text{8}\). Recently, Motovska et al.\(^2\)\(^\text{8}\), reported cigarette smoking as an independently associated factor with a prompt antiplatelet response to clopidogrel in patients with stable coronary artery disease undergoing elective percutaneous coronary intervention. Schedel et al.\(^2\)\(^\text{8}\), found clear evidence that agonist binding to platelet nACHR\(^\text{7}\) receptors elicits Ca\(^{2+}\) influx and enhanced fibrinogen receptor activation. Nicotine is a major constituent of cigarette smoke and also a selective cholinergic agonist. Contrastively, in a recent randomised perspective study\(^1\)\(^\text{8}\), current smokers significantly showed higher rates of procedure-related thromboembolism (\(p<0.001\)), and clopidogrel premedication failed to modify the risk of them in patients with unruptured intracranial aneurysms treated with coil embolization. Can we recommend smoking to enhance clopidogrel efficacy?

Our study had some limitations including small sample size, no randomized design, which could lead to some unexpected bias and lack of aspirin resistance. Most of all, clopidogrel resistance was not definitely defined yet and there was no standardized laboratory method to measure platelet inhibition rate. Further studies are needed to define clopidogrel resistance for Asian, especially for Korean and to find relationships between clopidogrel resistance and clinical outcome.

**CONCLUSION**

There was relatively high prevalence of clopidogrel resistance in patients with atherosclerotic cerebrovascular disease. Hypercholesterolemia was an independent predictive factor of clopidogrel resistance. Acute in-stent thrombosis was more frequently seen in the clopidogrel resistant group. Therefore, clopidogrel resistance test should be done to avoid thromboembolic complications related to stent-assisted angioplasty for atherosclerotic cerebrovascular disease, especially in patients with hypercholesterolemia and intracranial lesion.

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