

## Clinical Article

# Thromboxane A2 Synthetase Inhibitor Plus Low Dose Aspirin : Can It Be a Salvage Treatment in Acute Stroke Beyond Thrombolytic Time Window

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**Objective :** There is no proven regimen to reduce the severity of stroke in patients with acute cerebral infarction presenting beyond the thrombolytic time window. Ozagrel sodium, a selective thromboxane A2 synthetase inhibitor, has been known to suppress the development of infarction. The antiplatelet effect is improved when aspirin is used together with a thromboxane synthetase inhibitor.

**Methods :** Patients with non-cardiogenic acute ischemic stroke who were not eligible for thrombolysis were randomly assigned to two groups; one group received ozagrel sodium plus 100 mg of aspirin (group 1, n=43) and the other 100 mg of aspirin alone (group 2, n=43). Demographic data, cardiovascular risk factors, initial stroke severity [National Institute of Health Stroke Scale (NIHSS) and motor strength scale] and stroke subtypes were analyzed in each group. Clinical outcomes were analyzed by NIHSS and motor strength scale at 14 days after the onset of stroke.

**Results :** There were no significant differences in the mean age, gender proportion, the prevalence of cardiovascular risk factors, stroke subtypes, and baseline neurological severity between the two groups. However, the clinical outcome for group 1 was much better at 14 days after the onset of stroke compared to group 2 (NIHSS score,  $p=0.007$ , Motor strength scale score,  $p<0.001$ ). There was one case of hemorrhagic transformation in group 1, but there was no statistically significant difference in bleeding tendency between two groups.

**Conclusion :** In this preliminary study, thromboxane A2 synthetase inhibitor plus a low dose of aspirin seems to be safe and has a favorable outcome compared to aspirin alone in patients with acute ischemic stroke who presented beyond the thrombolytic time window.

**Key Words :** Thromboxane A2 synthetase · Stroke · Aspirin · Tissue Plasminogen activator.

## INTRODUCTION

Ozagrel sodium is a thromboxane A2 (TXA2) synthetase inhibitor<sup>3,8,14,25</sup>. TXA2 acts as a vasoconstrictor and platelet aggregator in the ischemic brain<sup>18</sup>. Ozagrel sodium reduces hypoperfusion and cerebral edema by restricting the generation of TXA2 while facilitating the generation of prostacyclin (PGI2). Due to this mechanism, ozagrel sodium has neuroprotective properties and it has been shown to have efficacy for motor recovery in animal models of cerebral ischemia<sup>3,8,14,25</sup>.

Although this product has been approved for clinical use in Korea and is widely used, its clinical efficacy in patients with acute ischemic stroke has not yet been studied. Therefore, the aim of this was to evaluate the safety, feasibility, and clinical efficacy of ozagrel sodium in acute ischemic stroke.

## MATERIALS AND METHODS

### Eligibility criteria

The patients with non-cardiogenic acute ischemic stroke who were not eligible for thrombolysis were randomly assigned to two groups; one group to receive ozagrel sodium plus 100 mg of aspirin (group 1, n=43) and the other to receive 100 mg of aspirin alone (group 2, n=43). The exclusion criteria were; 1) bleeding tendency in laboratory findings including patients with anti-coagulation therapy, 2) recent (<4 weeks) history of major operation, trauma, or intracranial hemorrhage, 3) the presence of a severe systemic illness at the time of the study, 4) ischemic strokes secondary to major medical events, invasive procedures, or surgeries, and 5) patients presenting symptoms longer than 2 days after the onset of symptoms or uncommunicative patients with an unknown time for the onset of symptoms.

### Initial assessment and management

Evaluation and treatment were done for all subjects according to the protocol of the National Institute of Neurological Disorders and Stroke<sup>26</sup>. When the patients came to the emergency

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room, the first action was to evaluate the state of their airways, breathing, and circulation followed by immediate intervention.

History taking and a physical examination including a full neurological examination was done. National Institute of Health Stroke Scale (NIHSS) scores and motor strength scale score were thoroughly measured upon admission. Baseline laboratory tests included serum glucose, electrolytes, renal/hepatic function, complete blood count, coagulation test, electrocardiography, and chest radiography. All patients underwent non-enhanced brain CT immediately after the initial neurologic examination and diffusion-weighted MR within 48 hours after admission. The stroke subtype was classified according to the TOAST classification<sup>1)</sup> and vascular risk factors (hypertension, diabetes mellitus, dyslipidemia, smoking, history of myocardial, and cerebral ischemia) were evaluated for each group.

All subjects received a low dose of aspirin (100 mg) within 48 hours from symptom onset. For group 1, ozagrel sodium was additionally administered within 48 hours of admission with a dosage of 80 mg twice a day, and the average administration period was 11.1 days.

**Outcome assessment**

The NIHSS score and motor strength scale score (on the day of admission and 14 days later) were evaluated and compared between the two groups. Adverse drug reactions and hemorrhagic complications such as gastrointestinal bleeding, hematuria, or hemorrhagic transformation were also evaluated.

**Statistical analysis**

SPSS 15.0 (SPSS Inc., Chicago, IL, USA) was utilized for the statistical analysis. The mean standard deviations or median

values were used as the basic risk factors while Fisher’s exact tests and chi-square tests were used to secure the significance of a single variable. Mann-Whitney U tests were used for category variables while student t-tests were used for the continuous variables within a *p*-value of 0.05. Gender, age, hypertension, diabetes mellitus, dyslipidemia, smoking, and a history of myocardial and cerebral ischemia are among the independent variables.

**RESULTS**

The average age of the subjects was 61.67 in group 1 and 60.44 in group 2. Group 1 consisted of 28 males and 15 females and group 2 had 29 males and 14 females. The prevalence of hypertension was 65.1% (28/43) in group 1 and 77.4% in group 2 (32/43). The prevalence of diabetes mellitus in group 1 and group 2 was 39.5% (17/43) and 20.9% (9/43), respectively. Dyslipidemia upon admission was present in 27.9% (12/43) of group 1 and 32.6% (14/43) of group 2. The percentage of smokers was 44.2% (19/43) and 62.8% (27/43) in group 1 and group 2, respectively. History of myocardial ischemia and cerebral ischemia was 7% and, 14% (3/43, 6/43) in group 1, and 9.3% and, 11.6% (4/43, 5/43) in group 2, respectively. None of these vascular risk factors were statistically significantly different between the two groups (Table 1).

According to the TOAST Classification, 20 subjects had large artery atherosclerosis and 23 had small vessel occlusions in group 1, while 22 subjects had large artery atherosclerosis and 21 subjects had small vessel occlusions in group 2. As mentioned in the eligibility criteria, cardioembolism was excluded during initial recruitment (Table 2).

The mean NIHSS score upon admission was 5.44 (range : 0-20) in group 1 and 5.19 (range : 1-13) in group 2. The mean motor power score upon admission in group 1 and group 2 was 3.56 and 3.81, respectively. Although there was no significant difference in the initial NIHSS score and motor power score, the mean NIHSS score measured two weeks later was 2.63 in group 1 and 3.88 in group 2, with more improvement in group 1 (*p*=0.007) (Fig. 1). In addition, the mean motor score measured two weeks later was 4.31 in group 1 and 3.88 in group 2, with respective changes of 0.74 and 0.07, indicating more improvement in motor power for group 1 (*p*<0.001) (Fig. 2).

One patient (1/43, 2.3%) in group 1 showed hemorrhagic transformation on the fourth day of admission, which resulted in a transient worsening of their mental status to a deep drowsy state. Four patients (4/43, 9.3%) in group 1

**Table 1.** Characteristics of the patients

Characteristics	Group 1 n=43, (%)	Group 2 n=43, (%)	<i>p</i> -value
Age (mean±SD*), years	61.67±12.59	60.44±13.32	0.660
Range, years	38-86	38-88	
Sex			0.820
Male	28 (65.1)	29 (67.4)	
Female	15 (34.9)	14 (32.6)	
Hypertension			0.348
Yes	28 (65.1)	32 (74.4)	
No	15 (34.9)	11 (25.6)	
Diabetes mellitus			0.060
Yes	17 (39.5)	9 (20.9)	
No	26 (60.5)	34 (79.1)	
Dyslipidemia			0.488
Yes	12 (27.9)	14 (32.6)	
No	31 (72.1)	29 (67.4)	
Smoking			0.084
Yes	19 (44.2)	27 (62.8)	
No	24 (55.8)	16 (37.2)	

\*Standard deviation

and two patients (2/43, 4.7%) in group 2 showed micro-hematuria, although no one showed gross hematuria in any of groups. All those with micro-hematuria had indwelling urinary catheters. There was no gastrointestinal bleeding in any of groups (Table 3).

There was no adverse drug reaction for group 1 subjects except that two of subjects (2/43, 4.6%) showed slight increases in their glutamic oxaloacetate transaminase and glutamic pyruvate transaminase values. No one suffered from nausea, vomiting, diarrhea, or constipation. The complete blood count, blood urea nitrogen, and creatine values of all the patients were normal. No one complained of drug fever, hair loss, or any pain in the areas through which the drug was administered.

## DISCUSSION

Ischemic stroke has been one of the leading causes of morbidity and mortality worldwide<sup>16</sup>. To reduce tissue damage from acute cerebral ischemia and to improve the neurological status of patients, cerebral reperfusion therapy including intravenous tissue plasminogen activator and intra-arterial thrombolysis within an eligible time window has been widely accepted<sup>2,4,5,7,9-11,17,27</sup>. However, the actual rate of giving intravenous or intra-arterial thrombolysis to patients who visit an emergency room is sadly low, since most patients fail to enter the hospital within the time window. Much research has been done to improve the long-term functional outcome of patients with ischemic stroke who have passed the time window<sup>20,28</sup>, however, the clinical implications have not been realized yet.

Brain damage by cerebral infarction occurs not only during an ischemic period but also after reperfusion takes place. Increased TXA<sub>2</sub> in brain tissue after cerebral reperfusion reduces the cerebral blood flow by promoting vasoconstriction and platelet aggregation<sup>25</sup>. On the other hand, PGI<sub>2</sub> expands blood vessels, prevents platelet aggregation, and plays an important role in controlling cerebral vasospasms<sup>12,22</sup>. Ozagrel sodium, a selective TXA<sub>2</sub> synthetase inhibitor, reduces the TXA<sub>2</sub> levels and increases the PGI<sub>2</sub> levels<sup>14,25</sup> whereas aspirin reduces both PGI<sub>2</sub> and TXA<sub>2</sub> as a cyclooxygenase inhibitor<sup>13</sup>. Therefore, Ozagrel sodium theoretically prevents a decrease in the cerebral blood flow during an ischemic period<sup>14,23</sup> and improves the delayed hypoperfusion during the reperfusion period<sup>24,25</sup>.

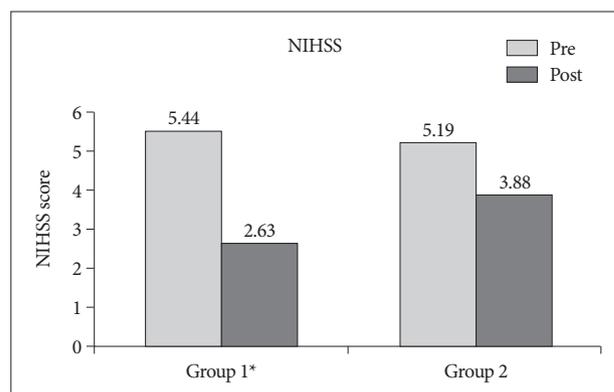
Aspirin curbs the generation of cyclooxygenase, which decreases the formation of TXA<sub>2</sub> and PGI<sub>2</sub><sup>13</sup>. Such sensitivity by platelet aggregation-related activity increases when a low dose of aspirin is used<sup>3</sup>. In contrast, the thromboxane synthetase inhibitor depresses the generation of TXA<sub>2</sub> by preventing endoperoxide utilization. The antiplatelet effect depends on how ef-

**Table 2.** Stroke subtype classification

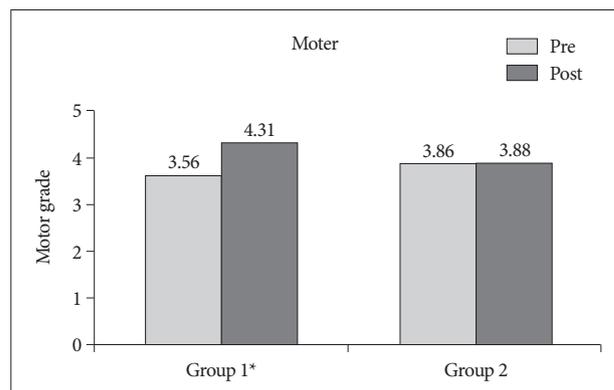
TOAST classification	Group 1 (n=43)	Group 2 (n=43)	p-value
Large artery atherosclerosis	20	22	0.457
Cardioembolism			
Small vessel occlusion	23	21	0.496
Stroke of other determined etiology			
Stroke of undetermined etiology			

**Table 3.** Hemorrhagic complications

	Group 1 (n=43)	Group 2 (n=43)	p-value
Micro-hematuria	2	4	0.676
Hemorrhagic transformation	0	1	1.000
Gastro-intestinal bleeding	0	0	1.000



**Fig. 1.** Comparison of mean NIHSS scores between treatment with thromboxane A2 synthetase inhibitor with a low dose of aspirin (group 1) and aspirin alone (group 2). pre : initial NIHSS score, post : NIHSS score at 14 days after onset of symptoms,  $p < 0.007$ . NIHSS : National Institute of Health Stroke Scale.



**Fig. 2.** Comparison of mean motor power score between treatment with thromboxane A2 synthetase inhibitor with a low dose of aspirin (group 1) and aspirin alone (group 2). pre : initial NIHSS score, post : NIHSS score at 14 days after onset of symptoms,  $p < 0.001$ . NIHSS : National Institute of Health Stroke Scale.

fectively the two types of prostaglandin metabolism are reduced. The combined therapy of a thromboxane synthetase inhibitor and aspirin produces the best effect by restraining the platelet aggregation response and TXA<sub>2</sub> synthesis and encouraging PGI<sub>2</sub> formation<sup>15</sup>. Due to the differentiated antagonism of the two medications on prostaglandin, the combined therapy of a

low dose of aspirin and a thromboxane synthetase inhibitor can be an effective antithrombotic treatment. Moreover, the synergistic effect by the two medications is more powerful in producing an antiplatelet effect compared to when each of them is used separately<sup>15</sup>.

A brain afflicted by cerebral infarction develops cytotoxic edema. The condition of brain edema itself causes brain damage and doubles the brain damage after cerebral infarction by reducing the cerebral blood flow during the reperfusion period<sup>19</sup>. Ozagrel sodium reduces brain swelling by acting during both the ischemic and reperfusion periods. It also prevents an expansion of cerebral infarction by curbing brain cell death in the penumbra<sup>6,14,18,21</sup>. For these reasons, ozagrel sodium can provide an additional effect to aspirin<sup>21</sup>.

Ozagrel sodium, a selective TXA2 synthetase inhibitor, was approved by the Korean Food and Drug Administration for use in cerebral ischemia with motor deficit and it has been a familiar drug with the members of the Korean neurological and neurosurgical society. However, there have been few clinical studies regarding its efficacy in ischemic stroke. This study reaffirmed the effects of ozagrel sodium, which have been proven through a previously described animal test. Through vasodilatation, restraint of platelet aggregation, and a decrease in brain swelling, ozagrel sodium prevents hypoperfusion. In this study, patients with acute cerebral infarction had a better NIHSS score and motor power score when treated with ozagrel sodium and aspirin together compared to those who were treated only with aspirin. There was no major adverse reaction to the drugs or hemorrhagic tendency except for one case of hemorrhagic transformation. However, that case had a large area of middle cerebral arterial territorial infarction with a high risk of hemorrhagic transformation in its natural course. The authors could not find any clue of whether this event resulted from the use of the TXA2 synthetase inhibitor or not.

Our study has several limitations such as a small number of patients and a short term follow up period. Thus, a further larger study may be necessary to prove the efficacy of the combination therapy of ozagrel sodium and aspirin at low doses.

## CONCLUSION

The combination therapy of ozagrel sodium and aspirin at low doses is safe, feasible, and effective in the treatment of acute cerebral infarction beyond the thrombolytic time window. It could especially help to improve motor functional outcome in the short term period. Further study on a larger scale might be needed to determine the long term outcomes.

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