Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.1209-22
Intern Med 62: 2959-2964, 2023
http://internmed.jp

【 ORIGINAL ARTICLE 】

Efficacy of Treatment with and without Initial Clopidogrel Loading in Branch Atheromatous Disease

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Abstract:

Objective Despite aggressive therapeutic interventions during the acute phase of branch atheromatous disease (BAD)-type cerebral infarction, many patients, even those with a mild condition at the onset, experience neurological deterioration after hospitalization and develop serious deficits. We compared the therapeutic efficacy of multiple antithrombotic therapies for BAD between patients who received a clopidogrel loading dose (loading group; LG) and those without loading (non-loading group; NLG).

Patients Between January 2019 and May 2022, patients with BAD-type cerebral infarction in the lenticulostriate artery admitted within 24 h of the onset were recruited. This study included 95 consecutive patients who received combination argatroban and dual antiplatelet therapy (aspirin and clopidogrel).

Methods Patients were classified into the LG and NLG according to whether or not a loading dose of clopidogrel (300 mg) had been administered on admission. Changes in neurological severity [National Institutes of Health Stroke Scale (NIHSS) score] during the acute phase were retrospectively evaluated.

Results There were 34 (36%) and 61 (64%) patients in the LG and NLG, respectively. On admission, the median NIHSS score was similar between the groups [LG: 2.5 (2-4) vs. NLG: 3 (2-4), p=0.771]. At 48 h following admission, the median NIHSS scores were 1 (0.25-4), and 2 (1-5) in the LG and NLG, respectively (p=0.045). Early neurological deterioration (END; defined as worsening of the NIHSS score by ≥4 points at 48 h after admission) occurred in 3% of LG and 20% of NLG patients (p=0.028).

Conclusion Administration of a clopidogrel loading dose with combination antithrombotic therapy for BAD reduced END.

Key words: ischemic stroke, branch atheromatous disease, clopidogrel, loading, neurological deterioration

(Intern Med 62: 2959-2964, 2023)
(DOI: 10.2169/internalmedicine.1209-22)

Introduction

Many patients with branch atheromatous disease (BAD)-type cerebral infarction, even those with a mild condition at the onset, experience neurological deterioration after hospitalization and develop serious deficits (1-4). Therefore, aggressive antithrombotic therapy should be considered at presentation during the acute phase of BAD.

Since arteriosclerosis underlies the pathology of BAD, dual antiplatelet therapy (DAPT) combining two antiplatelet drugs can potentially prevent progression of the disease and is often administered in clinical settings (5-8). The guidelines also strongly recommend the administration of DAPT with aspirin and clopidogrel for non-cardioembolic ischemic stroke within 24 h of the onset (9).

The mechanism underlying symptom progression in BAD is believed to be associated with fibrin clots. In Japan, when BAD is diagnosed, a prevalent therapeutic strategy is antithrombotic therapy using multiple agents, including the anticoagulant argatroban (a selective synthetic thrombin inhibitor), in addition to DAPT (6, 7). Indeed, argatroban is administered to 78.4% of patients with BAD and 68.4% with DAPT in clinical practice in Japan (10).

Clopidogrel therapy initiated with a loading dose of 300 mg was approved to prevent recurrence of "non-cardiogenic cerebral infarction in the acute phase" in Japan in 2018. Clopidogrel is metabolized in two stages by cytochrome

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Received: October 27, 2022; Accepted: February 1, 2023; Advance Publication by J-STAGE: March 8, 2023
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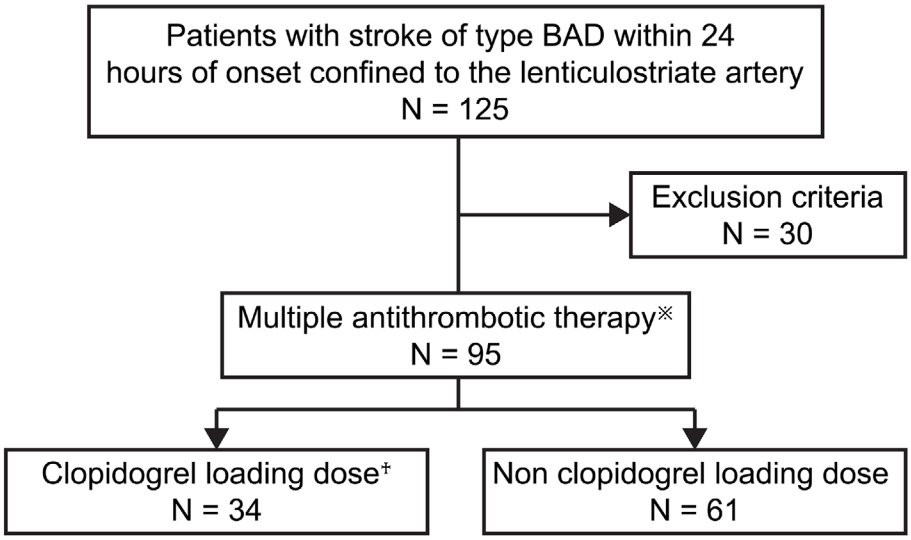

Figure 1. Baseline characteristics of patients in the clopidogrel loading and non-loading groups. ※Argatroban: 60 mg/day for 2 days, followed by 10 mg twice daily for 5 days). Aspirin: 100 mg/day. Clopidogrel: 75 mg/day. †300 mg on day 1, followed by 75 mg once daily.

P450; therefore, clopidogrel exhibits a delayed onset of action. However, this delay can be mitigated via the administration of an initial clopidogrel loading dose (11). However, another study on BAD with a smaller sample size reported that administering clopidogrel loading doses did not prevent neurological deterioration (12).

In the present study, we examined the therapeutic efficacy of intensive treatment whereby a clopidogrel loading dose was added to multiple antithrombotic therapies (DAPT+argatroban).

Material and Methods

Between January 2019 and May 2022, 125 patients with BAD-type cerebral infarction in the lenticulostriate artery (LSA) were admitted to our department within 24 h of the onset. This study included 95 consecutive patients who received combination therapy with argatroban and DAPT and had been independent in their activities of daily living with a modified Rankin Scale (mRS) score of ≤1 before admission.

The patients were classified into the loading group (LG), who received an initial clopidogrel loading dose of 300 mg on the day of admission, and those without loading (the non-loading group; NLG) (Fig. 1). BAD was defined based on diffusion-weighted imaging at the time of arrival as infarction involving ≥3 horizontal slices (section thickness/intersection gap, 5/1.5 mm) in the LSA territory and on magnetic resonance angiography as no stenosis (≥50%) or occlusion of a major artery of the branch artery and no cardioembolic source (e.g. atrial fibrillation) (1, 3).

This study was also designed to evaluate the effect of clopidogrel loading. Therefore, DAPT was limited to the combined usage of aspirin and clopidogrel, and patients who used other combinations, such as aspirin+cilostazol, clopidogrel+cilostazol, or ozagrel sodium (an intravenous antiplatelet drug), were excluded. In addition, patients who used anticoagulants other than argatroban or who received thrombolytic therapy were also excluded from the study. Aspirin was used at a fixed dose of 100 mg per day from the start of treatment.

Between the LG and NLG, we compared the age, sex, risk factors for cerebral infarction (hypertension, diabetes mellitus, hyperlipidemia, and smoking history), history of previous ischemic stroke, history of coronary artery disease, body weight (BW), laboratory test results on admission [blood glucose level (BG), hemoglobin A1c level (HbA1c), creatinine (Cr), creatinine clearance (CrCl) calculated using the Cockcroft-Gault equation (13), triglyceride (TG), total cholesterol (T-CHO), low-density lipoprotein cholesterol (LDL-C)], blood pressure (systolic and diastolic) on admission, antithrombotic drug use at the time of the stroke onset, National Institutes of Health Stroke Scale (NIHSS) score (on admission, 48 h after admission, and 1 week after admission) (14), infarct volume, rate of statin (HMG CoA reductase inhibitors) and edaravone (free radical scavenger) use, duration of hospital stay, occurrence of symptomatic intracerebral hemorrhaging (sICH), and clinical outcomes at hospital discharge.

Neurological deterioration was classified as early neurological deterioration (END) ΔN4 when the NIHSS score at 48 h worsened by ≥4 points compared to the score on admission and ENDΔN1 when the NIHSS score worsened by ≥1 point. The infarct volume of the selected slice with the largest number of lesions visually observed from diffusion weighted imaging (DWI) was measured using the ABC/2 method (15, 16): 0.5×diameter of the length×diameter of the width×(0.5×number of DWI slices of acute infarction). sICH was defined as ICH associated with worsening of any neurological symptom (17). Clinical outcomes were assessed us-

Table. Patient Characteristics of Loading and Non-loading Groups.

	Loading group (n=34)	Non-loading group (n=61)	p value
Age, years	71.8±13.3	71.7±11.2	0.958
Female sex, no. (%)	13 (38)	29 (48)	0.399
Hypertension, no. (%)	22 (65)	50 (82)	0.081
Diabetes mellitus, no. (%)	9 (26)	23 (38)	0.366
Hyperlipidemia, no. (%)	16 (47)	29 (48)	1.000
Coronary heart disease, no. (%)	4 (12)	6 (10)	0.742
Cerebral infarction, no. (%)	5 (15)	6 (10)	0.515
Smoking history, no. (%)	6 (18)	14 (23)	0.609
Systolic blood pressure, mmHg	180.9±30.9	191.3±30.8	0.118
Diastolic blood pressure, mmHg	97.7±16.6	95.4±21.3	0.584
BW, kg	61.8±13.9	58.7±11.8	0.261
Glucose level, mg/dL	135.9±70.3	144.8±77.8	0.582
Hemoglobin A1c, %	6.1±1.6	6.4±1.7	0.315
Creatinine, mg/dL	1.07±1.43	0.85±0.60	0.283
Creatinine clearance, mL/min	72.6±37.4	73.7±31.2	0.879
Triglyceride, mg/dL	116.0±50.3	130.0±74.3	0.268
Total cholesterol, mg/dL	208.0±49.7	219.0±51.7	0.462
Low-density lipoprotein cholesterol, mg/dL	144.0±40.1	139.0±42.8	0.581
NIHSS score on admission	2.5 (2-4)	3 (2-4)	0.771
Infarct volume, mL	1.08±1.71	0.91±1.06	0.548
Treatment with antithrombotic drugs on admission	5 (18)	7 (11)	0.750
Aspirin	2	4	
Clopidogrel	2	3	
Cilostazol	1		
Concomitant medication			
Statin, no. (%)	27 (79)	39 (64)	0.163
Edaravone, no. (%)	30 (88)	55 (90)	0.742
Duration of hospitalization, days	17.5 (14.25-28)	19 (12-29)	0.855

Data are shown as mean±SD, median (interquartile range), or number (%). BA: basilar artery, BMI: body mass index, BW: body weight, DWI-ASPECTS: Alberta stroke program early computed tomography score on diffusion-weighted imaging, ICA: internal carotid artery, MCA: middle cerebral artery, NIHSS: National Institutes of Health Stroke Scale, rt-PA: recombinant tissue plasminogen activator

ing the mRS score at discharge (18).

This retrospective study was approved by the Human Research Ethics Committee of Saitama Medical University International Medical Center (approval No: 2022-50).

Statistical analyses

Data were analyzed using the IBM SPSS Statistics software program for Windows, version 20.0 (IBM, Armonk, USA). The age, systolic/diastolic blood pressure, BW, HbA1c, TG, T-CHO, LDL-C, BG, Cr, and CrCl values and the infarct volume were compared between groups using Student's *t*-test. The NIHSS score, duration of hospital stay, and mRS scores were compared using the Mann-Whitney U test, and ratios were compared using Fisher's exact test (two-sided). p values <0.05 were considered statistically significant.

Results

Table summarizes the patient characteristics of the LG and NLG. There were 34 (36%) and 61 (64%) patients in the LG and NLG, respectively. There were no significant between-group differences in background factors, such as the age, sex, NIHSS score on admission, or infarct volume. Changes in the NIHSS score are shown in Fig. 2. The NIHSS score was significantly lower in the LG than in the NLG at 48 h after admission [median (interquartile range (IQR)) LG: 1 (0.25-4) vs. NLG: 2 (1-5), p=0.045]. The NIHSS score at 1 week after admission was lower in the LG than in the NLG but not to a significant degree [LG: 1 (0-3.75) vs. NLG: 2 (1-6); p=0.083]. The limb movement items (NIHSS scores 0-8) were compared at admission and 48 h after admission. The NIHSS scores at admission did not differ markedly between the groups [LG: 2 (2-2.75) vs. NLG: 2 (2-3); p=0.217], but the NIHSS score at 48 h was significantly lower in the LG than in the NLG [LG: 1 (0.25-2) vs. NLG: 2 (1-4); p=0.009]. In contrast, there was no significant difference between the two groups in the NIHSS score, excluding the limb movement items on admission and 48 h after admission [on admission, LG: 0 (0-1) vs. NLG: 0 (0-1); p=0.324, 48 h after admission, LG: 0 (0-1) vs. NLG: 0 (0-1); p=0.909].

ENDΔN1 was less frequent in the NLG than in the LG

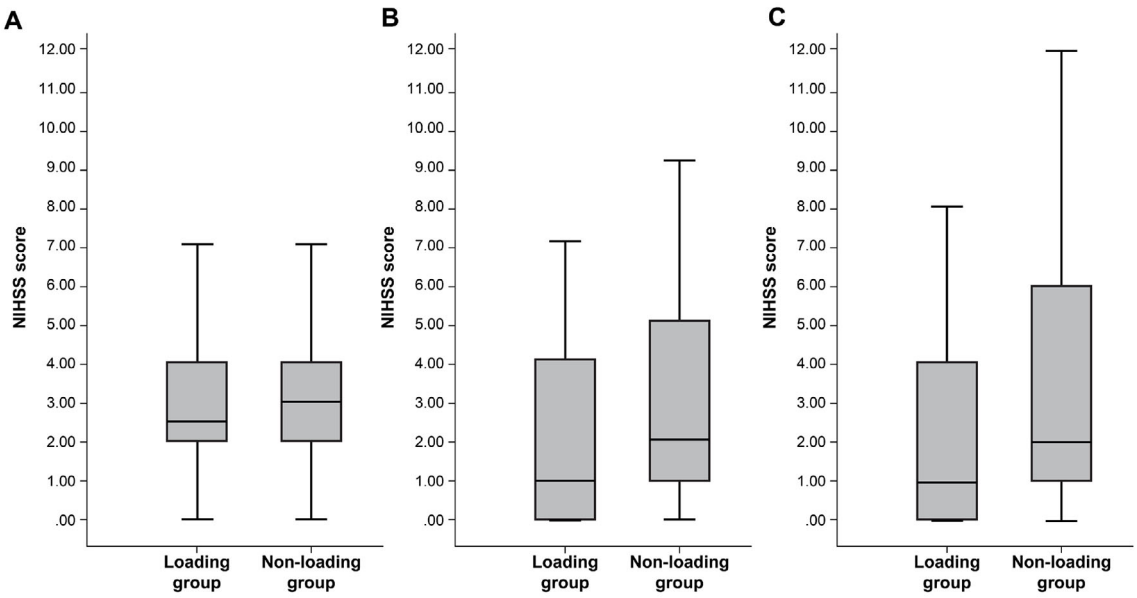

Figure 2. **Changes in the National Institutes of Health Stroke Scale (NIHSS) score. (A) On admission, (B) 48 h after admission, and (C) 1 week after admission. The NIHSS score was significantly lower in the loading group than in the non-loading group at 48 h following admission. Data are presented as the median (interquartile ranges) [on admission: 2.5 (2-4) vs. 3 (2-4), p=0.771; 48 h after admission: 1 (0.25-4) vs. 2 (1-5), p=0.045; 1 week after admission: 1 (0-3.75) vs. 2 (1-6), p=0.083].**

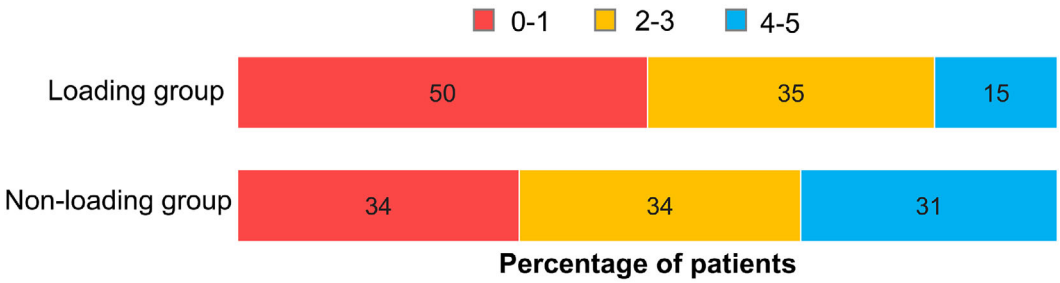

Figure 3. **Modified Rankin Scale (mRS) score. At hospital discharge, patients with an mRS score of 0-1 comprised 50.0% (17 of 34 patients) of the loading group and 34.4% (21 of 61 patients) of the non-loading group. The outcomes showed no significant between-group difference (p=0.190).**

(18% in the LG and 31% in the NLG) but not to a significant degree (p=0.244). In contrast, the rate of ENDΔN4 was 3% in the LG and 20% in the NLG, showing significantly less deterioration of the NIHSS score ≥4 points in the LG than in the NLG (p=0.028).

Fig. 3 shows the mRS score at discharge. The proportion of patients with mRS 0-1 at discharge was 50% in the LG and 34% in the NLG, showing no significant difference (p=0.190); however, the LG had a higher proportion of patients with a favorable outcome than the NLG. There was no sICH in either group.

Discussion

The results of this study demonstrated that multiple antithrombotic therapies (DAPT+argatroban), which are currently believed to be the most potent therapies for BAD occurring in the LSA territory, significantly reduced END (especially worsening of movement symptoms) when these therapies were administered in combination with an initial loading of clopidogrel, compared with their administration alone.

When clopidogrel is administered at an initial loading dose of 300 mg in combination with aspirin, the antithrombotic effect appears within 90 min of the initial administration, reaches potency at 6 h following the initial administration (61% and 75% of platelet and fibrin reduction, respectively), and subsequently achieve steady state. Initial administration of a clopidogrel loading dose of 300 mg accelerated the onset of the antithrombotic effect of combination therapy with clopidogrel and acetylsalicylic acid (11).

BAD is characterized by END, and symptom progression up to three days after the onset is reportedly a factor associated with a poor prognosis (19). Therefore, it is important to aggressively treat BAD in order to prevent symptom progression during the early stages. The results of the present

study suggest that the administration of clopidogrel loading doses led to the onset of a potent antithrombotic effect, which contributed to the prevention of symptom progression in the early stages after the onset.

However, the prevalence of CYP2C19*2 and *3 polymorphisms, which are associated with poor antithrombotic agent metabolizers, is higher in the Japanese population (approximate prevalence of 20%) than in Europeans and Americans (20, 21). CYP2C19 polymorphisms strongly affect the antiplatelet action of clopidogrel, which has been demonstrated in the real-world setting. A previous report showed that the clopidogrel loading effects on pharmacokinetics vary among CYP2C19 genetic polymorphisms (22). Since this study cannot rule out the possibility of genetic polymorphisms affecting the therapeutic effects, the impact of genetic polymorphisms needs to be verified in future studies.

Several limitations associated with the present study warrant mention. First, we used a retrospective study design to obtain data. Second, the included cohort was small. Third, the base therapy was limited to DAPT (aspirin+clopidogrel) plus argatroban, and this therapy was not compared with other combination therapies. Finally, only BAD localized in the LSA territory was targeted; therefore, other types of BAD, such as that occurring in the paramedian pontine artery territory, were not examined.

There is no clear evidence concerning the efficacy and safety of BAD treatment, and no therapeutic strategies have yet been established. However, the present findings suggest that the addition of clopidogrel loading doses to conventional multiple antithrombotic therapy for BAD might prevent END compared with therapy without clopidogrel loading doses. The further accumulation of cases and detailed investigation of various treatments, including the loading effect of clopidogrel on BAD, will facilitate the development of more effective therapeutic strategies for BAD.

Conclusion

The combination of clopidogrel initial loading with multiple antithrombotic therapies using DAPT (aspirin+clopidogrel) plus argatroban for BAD occurring in the LSA territory may prevent symptom progression effectively in the early stages after the onset.

The authors state that they have no Conflict of Interest (COI).

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