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Short-term Bleeding Events Observed with Clopidogrel Loading in Acute Ischemic Stroke Patients

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Abstract

Introduction—The Fast Assessment of Stroke and Transient Ischemic Attack to Prevent Early Recurrence trial raised concern that loading doses of clopidogrel may increase hemorrhagic complications. We investigated if similar rates of hemorrhage occur in patients with acute ischemic stroke (AIS) of varying severity.

Methods—Patients meeting inclusion criteria were divided into 2 groups: the LOAD group and non-LOAD group. The LOAD group was defined as patients who were administered a loading dose of 300 mg or more of clopidogrel with or without aspirin within 24 hours of admission. The non-LOAD group was devised using propensity score (PS): 55 patients who received a loading dose of clopidogrel of 300 mg or more were matched on PS to 55 patients who did not receive loading doses. These patients were taken from a pool of 341 consecutive ischemic patients ineligible for intravenous or intra-arterial fibrinolysis, 162 of whom received a clopidogrel loading dose and the remainder of whom did not. The frequency of hemorrhage was compared between the 2 groups using Student *t* test and chi-square. Logistic regression was used to assess the

relationship between loading dose and serious bleeding events (symptomatic intracerebral hemorrhage [sICH] or transfusion for systemic bleeding).

Results—AIS patients (N = 596) were screened during the 31-month period of this retrospective study. Of this sample, 170 patients were excluded: 149 patients were excluded because they were treated with intravenous tissue plasminogen activator (IV t-PA) alone, 11 were excluded because they were treated with IV t-PA combined with intra-arterial therapy (IAT), and 10 were excluded for treatment with IAT alone. An additional 85 patients were excluded because they were not admitted to the stroke service or because they had an in-hospital stroke. Baseline characteristics of the groups were well matched. There were no significant differences in the rates of sICH, transfusion, hemorrhagic transformation, or systemic bleeding. Clopidogrel loading was not associated with increased odds of serious bleeding events in the crude model (odds ratio [OR] .92, 95% confidence interval [CI] .27-3.13) or after adjusting for covariates and confounders of interest (OR 1.06, 95% CI .28-4.04).

Discussion—Contrary to our original hypothesis, patients with AIS receiving clopidogrel loading doses within 24 hours of symptom onset did not appear to experience a higher rate of new serious bleeding events during acute hospitalization when compared with patients who did not receive loading doses. The Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke trial is expected to provide insight into the safety of clopidogrel loading as an acute intervention after cerebral ischemia.

Keywords

Acute stroke; clopidogrel; loading; antiplatelet; hemorrhage

Introduction

Given the high incidence of recurrence and progression during the early stages of ischemic stroke, achieving early maximum platelet inhibition may be an important strategy for preventing neurologic deterioration. Although there is evidence to support aspirin therapy within the first 48 hours after the onset of acute ischemic stroke (AIS), the absolute risk reduction for recurrent stroke is less than 1%.¹ Studies support the use of dual antiplatelet therapy (clopidogrel and aspirin) at high “loading” doses in other vascular occlusive diseases (ie, acute myocardial infarction) and with percutaneous coronary interventions.²⁻⁷ However, the benefits of platelet inhibition on reducing major vascular events after stroke may be offset by the risk of hemorrhagic complications.

Although previous studies have reported increased bleeding in stroke patients treated with dual antiplatelet therapy,⁸ limited safety data exist for patients treated during the acute period. A small retrospective review comparing patients with AIS or transient ischemic attack (TIA) who received loading doses of clopidogrel and aspirin to historical controls reported low rates of systemic and intracranial hemorrhage.⁹ In a pilot study where patients were randomized within 24 hours of symptom onset to placebo or clopidogrel loading, the latter demonstrated a protective effect on stroke recurrence at the cost of increased bleeding.¹⁰ However, this study was conducted in patients with TIA or mild stroke. We investigated rates of bleeding in patients with AIS of varying severity. We hypothesized that

clopidogrel loading for more severe strokes would be associated with higher rates of bleeding.

Methods

Study Participants

After approval by our Institutional Review Board, consecutive AIS patients who were admitted to the Tulane Stroke Service within 24 hours of symptom onset between June 2008 and December 2010 were screened. Patients who experienced in-house strokes or patients who were treated with intravenous tissue plasminogen activator (IV t-PA) or intra-arterial therapy (IAT) were excluded. Patients meeting inclusion criteria were divided into 2 groups: the LOAD group and the non-LOAD group. The LOAD group was defined as patients who were administered a loading dose of 300 mg or more of clopidogrel with or without aspirin within the first 24 hours of admission. The aim was to quickly inhibit platelets in patients who presented early, but were not candidates for thrombolysis, and who we thought were at higher risk for stroke progression (suspected small vessel strokes and large vessel occlusions without territorial completed infarcts on baseline imaging). The non-LOAD group was defined as patients who were not administered a loading dose of clopidogrel.

Variables

Data on baseline demographics and clinical and imaging characteristics were collected prospectively as part of the Tulane Stroke Registry.¹¹ Stroke severity was measured by the National Institutes of Health Stroke Scale (NIHSS). Stroke mechanism was determined using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.¹² A retrospective review of computed tomography and magnetic resonance imaging scans of the head was conducted by a blinded rater to assess for intracranial hemorrhage according to the European Cooperative Acute Stroke Study criteria.¹³ Symptomatic intracerebral hemorrhage (sICH) was defined as a PH-1 or PH-2 with increase in NIHSS greater than or equal to 4 points. Inpatient records were reviewed to determine if systemic bleeding occurred or if transfusion was performed during hospitalization. The composite end point of a new serious bleeding event was defined as either bleeding necessitating transfusion or sICH.

Study Design and Statistical Analysis

Data determined to be missing at random were addressed using multiple imputation techniques. Five data sets were generated. As exposure to clopidogrel loading was not based on random allocation, it was anticipated that the 2 exposure groups would not be comparable with respect to key covariates. We used propensity score (PS) methods to match exposed patients (received a clopidogrel loading dose, LOAD) to unexposed patients (did not receive a clopidogrel loading dose, non-LOAD) with the primary objective of maximizing the balance in the distribution in possible confounders between patients receiving clopidogrel loading doses and patients not receiving loading doses. The PS model was constructed with multivariable logistic regression, with exposure to clopidogrel loading as the binomial dependent variable and a wide range of clinical and demographic variables including demographics, health insurance status, medical history, and home medications (eg, for hypertension, hypercholesterolemia, and diabetes) as the predictor variables. The PS model

was used to calculate the PS for each patient. A 5 → 1 computerized greedy matching technique where exposed patients were first matched to unexposed patients who had a PS that was identical in all 5 digits was employed.¹⁴ Those who did not match were then matched to controls on 4 digits of the PS, continuing down to a 1-digit match on PS for those who remained unmatched. Measured covariates and outcomes in the PS-matched sample were compared between exposure groups using Pearson chi-squared or independent sample Student *t* test where appropriate.

Seven additional multivariable models were constructed, in addition to the baseline model. This was performed to determine whether the PS-matched groups differed from the overall group regarding serious bleeding events. The first model used the full sample and did not include additional covariates. The second included the full sample with PS as a covariate. The third model included the full sample, NIHSS, age, and admission glucose. The fourth model used the full sample, PS, NIHSS, age, and admission glucose. The fifth model included the PS-matched sample with no covariates. The sixth model performed on the PS-matched sample included only PS as a covariate. The seventh model performed on the PS-matched sample included age, admission glucose, and NIHSS on admission. The eighth and final model performed on the PS-matched sample included PS, age, admission glucose, and NIHSS on admission. Point estimates, confidence intervals, and *P* values were calculated using the SAS procedure MIANALYZE. Analyses were carried out in SAS version 9.02 (SAS Institute, Cary, NC).

Results

In total, 596 AIS patients were screened during the 31-month period. Of this sample, 170 patients were excluded: 149 patients were excluded because they were treated with IV t-PA alone, 11 patients were excluded because they were treated with IV t-PA combined with IAT, and 10 were excluded for treatment with IAT alone. An additional 85 patients were excluded because they were not admitted to the stroke service or because they had an in-hospital stroke. Using PS, 55 patients who received a loading dose of clopidogrel were matched to 55 patients who did not receive a loading dose from a pool of 341 eligible patients, 162 of whom received a clopidogrel loading dose and the remainder of whom did not receive a clopidogrel loading dose.

Baseline characteristics of the PS-matched LOAD and non-LOAD groups are shown in Table 1. There were no significant differences between groups; however, the group that received a loading dose of clopidogrel contained nonsignificantly higher proportions of blacks, hemosiderin deposits seen on magnetic resonance imaging gradient echo imaging, and stroke of cardioembolic etiology.

As depicted in Table 2, there were no significant differences in the rates of sICH, systemic bleeding requiring transfusion, or systemic bleeding not requiring transfusion between PS-matched groups. Non-LOAD patients exhibited a nonsignificant but slightly higher rate of hemorrhagic transformation (*P* = .0820).

Table 3 illustrates the odds of having a new bleeding event for LOAD patients when compared with non-LOAD patients using each of the 8 models. Clopidogrel loading was not associated with an increase in the odds of having a new serious bleeding event in the PS-matched sample (odds ratio [OR] .92, 95% confidence interval [CI] .27-3.13). Adjusting for PS had little effect on the point estimate and confidence intervals (OR .91, 95% CI .26-3.14). When age, glucose, and NIHSS on admission were added to the model, the odds of having a new bleeding event following clopidogrel loading remained nonsignificant, although the 95% CI was slightly wider (OR 1.04, 95% CI .28-3.90). Similar results were seen when PS was added to the model (OR 1.06, 95% CI .28-4.04).

Discussion

Contrary to our original hypothesis, patients with AIS receiving clopidogrel loading doses within 24 hours of arrival did not appear to experience a higher rate of new serious bleeding events during acute hospitalization when compared with patients who did not receive loading doses. In contrast, the Fast Assessment of Stroke and Transient Ischemic Attack to Prevent Early Recurrence (FASTER) trial, which monitored patients for 90 days, reported higher rates of symptomatic bleeding events and higher rates of moderate-to-severe systemic bleeding when patients randomized to clopidogrel loading were compared with placebo.¹⁰

Differences observed in bleeding events may be partially because of differences in our patient samples. Patients receiving clopidogrel loading doses in the FASTER trial appear to have been slightly older and had a lower rate of previous stroke and history of coronary artery disease when compared with the patients in our sample that received loading doses.¹⁰ In addition, the majority of patients receiving clopidogrel loading doses in the FASTER trial were white. Patients randomized to clopidogrel loading in the FASTER trial had less severe strokes (median NIHSS 0.5) compared with patients in our sample exposed to clopidogrel loading (median NIHSS 4). This is an interesting finding as one would expect a higher hemorrhagic transformation in the group with higher stroke severity. Finally, the distribution of TOAST stroke mechanism appeared dissimilar. A cardioembolic etiology was identified in 27% of the LOAD patients in our sample, compared with only 5% of the patients receiving clopidogrel loading doses in the FASTER trial. Conversely, a small vessel etiology was identified in only 18% of our LOAD patients versus nearly 29% of the patients receiving clopidogrel loading doses in the FASTER trial.

Another possible explanation for the difference observed in bleeding events is the duration of dual antiplatelet therapy. Although patients in the FASTER trial were treated with dual antiplatelet therapy for 90 days,¹⁰ patients in our sample were treated with dual antiplatelets during the acute hospitalization only, after which only a single antiplatelet agent was continued. Unlike the FASTER trial that followed patients for 90 days, our study observed patients only during their initial hospitalization. This may have contributed to our finding that patients receiving clopidogrel loading doses within 24 hours of arrival did not appear to experience a higher rate of new serious bleeding events. However, as clopidogrel loading has been reported to rapidly achieve platelet inhibition, one would predict that any increased risk of bleeding with a loading dose, as opposed to standard initial dosing, would similarly be expected in the brief period during which platelets were being rapidly inhibited. The time

from treatment to serious hemorrhage in the FASTER trial was not reported, making it unclear if the hemorrhage rate is related to the initial loading or the treatment duration of 90 days.

The rate of new serious bleeding events observed in both our LOAD and non-LOAD groups is higher than previously reported in the Management of Atherothrombosis with Clopidogrel in High-risk Patients (MATCH) trial.⁸ Our higher rates of new serious bleeding events may be partially because of the timing of dual antiplatelet administration. Whereas patients in our sample received clopidogrel loading doses within 24 hours of arrival after presenting within 24 hours of stroke symptom onset, patients in MATCH were enrolled up to 90 days after their ischemic event (median 26-27 days). Although MATCH trial patients received dual antiplatelet therapy, they did not receive clopidogrel loading doses in the acute period. In addition, only 2%-3% of patients in the MATCH trial were found to have cardioembolic etiologies, as opposed to 22%-27% in our LOAD and non-LOAD groups. Previous studies have reported spontaneous hemorrhagic transformation rates as high as 25% in patients with cardioembolic strokes.¹⁵

We examined the potential increased risk of clopidogrel loading using a propensity-matched cohort. PS methods have been shown to improve our ability to identify actual treatment effects in the setting of treatment selection bias often seen in observational studies.¹⁶⁻¹⁸ Our PS-matched results are based on a subset of the total study population as patients who received clopidogrel loading doses and patients who did not receive loading doses that could not be matched on the basis of their PS are discarded from the matched analysis (66% LOAD group and 69% of non-LOAD group). We performed multiple models in the full sample and compared these results with our PS-matched sample in an effort to address this concern. Despite this, there are limitations associated with this study including the small sample size remaining after applying exclusions and PS matching. Our findings of a trend for more hemorrhagic transformations in the non-LOAD group may have been a function of sample size or a combination of baseline confounders we cannot account for but makes it unlikely that clopidogrel loading is harmful in our population we opted to treat. Additionally, we did not collect information on progression or fluctuation of neurological deficits that may have prompted the decision to clopidogrel load, and thus we are not able to account for this in the model.

Our results suggest that clopidogrel loading in AIS did not increase the odds of a serious bleeding event, regardless of whether the full sample or a smaller PS-matched sample was employed and regardless of whether demographic and clinical characteristics were taken into consideration. These findings, because of the retrospective observational nature of our study, are hypothesis generating. These findings support the need for randomized trials to confirm the safety of clopidogrel loading in AIS. We anxiously await the results of the Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke trial.¹⁹ This National Institute of Neurological Disorders and Stroke-sponsored prospective randomized clinical trial will provide insight into the safety and potential efficacy of clopidogrel loading in combination with aspirin as an acute intervention after cerebral ischemia.

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References

1. Chen ZM, Sandercock P, Pan HC, et al. Indications for early aspirin use in acute ischemic stroke: a combined analysis of 40,000 randomized patients from the Chinese Acute Stroke Trial and the International Stroke Trial. On behalf of the CAST and IST Collaborative Groups. *Stroke*. 2000; 31:1240–1249. [PubMed: 10835439]
2. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ*. 2002; 324:71–86. [PubMed: 11786451]
3. Akbulut M, Kutlu M, Ozbay Y, et al. Efficacy of clopidogrel on reperfusion and high-sensitivity C-reactive protein in patients with acute myocardial infarction. *Mediators Inflamm*. 2009; 2009:932515. [PubMed: 19365587]
4. Mehta SR, Yusuf S, Peters RJ, et al. Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial (CURE) Investigators. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet*. 2001; 358:527–533. [PubMed: 11520521]
5. Lemesle G, Delhaye C, Sudre A, et al. Impact of high loading and maintenance dose of clopidogrel within the first 15 days after percutaneous coronary intervention on patient outcome. *Am Heart J*. 2009; 157:375–382. [PubMed: 19185648]
6. Szuk T, Gyongyosi M, Homorodi N, et al. Effect of timing of clopidogrel administration on 30-day clinical outcomes: 300-mg loading dose immediately after coronary stenting versus pretreatment 6 to 24 hours before stenting in a large unselected patient cohort. *Am Heart J*. 2007; 153:289–295. [PubMed: 17239691]
7. Uchiyama S, Tanahashi N, Minematsu K. Clopidogrel Two Doses Comparative 1-Year Assessment of Safety and Efficacy (COMPASS) Study in Japanese patients with ischemic stroke. *Cerebrovasc Dis*. 2012; 34:229–239. [PubMed: 23018233]
8. Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blinded, placebo-controlled trial. *Lancet*. 2004; 364:331–337. [PubMed: 15276392]
9. Meyer DM, Albright KC, Allison TA, et al. LOAD: a pilot study of the safety of loading of aspirin and clopidogrel in acute ischemic stroke and transient ischemic attack. *J Stroke Cerebrovasc Dis*. 2008; 17:26–29. [PubMed: 18190818]
10. Kennedy J, Hill MD, Ryckborst KJ, et al. Fast Assessment of Stroke and Transient Ischaemic Attack to Prevent Early Recurrence (FASTER): a randomised controlled pilot trial. *Lancet Neurol*. 2007; 6:961–969. [PubMed: 17931979]
11. Albright KC, Martin-Schild S, Bockholt HJ, et al. No consensus on definition criteria for stroke registry common data elements. *Cerebrovasc Dis Extra*. 2011; 1:84–92. [PubMed: 22566986]
12. Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtypes of acute ischemic stroke. Definitions for use in multicenter clinical trial. *Stroke*. 1993; 24:35–41. [PubMed: 7678184]
13. Hacke W, Kaste M, Fieschi C, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. *JAMA*. 1995; 274:1017–1025. [PubMed: 7563451]
14. Parsons LS. Reducing Bias in a Propensity Score Matched-Pair Sample Using Greedy Matching Techniques. *SAS® Users Group International (SUGI)*. 2004; 26:214–226.

15. Kelley RE, Berger JR, Alter M, et al. Cerebral ischemia and atrial fibrillation: prospective study. *Neurology*. 1984; 34:1285–1291. [PubMed: 6541300]
16. Berger ML, Mamdani M, Atkins D, et al. Good research practices for comparative effectiveness research: defining, reporting and interpreting nonrandomized studies of treatment effects using secondary data sources: the ISPOR Good Research Practices for Retrospective Database Analysis Task Force Report—Part I. *Value Health*. 2009; 12:1044–1052. [PubMed: 19793072]
17. Stukel TA, Fisher ES, Wennberg DE, et al. Analysis of observational studies in the presence of treatment selection bias: effects of invasive cardiac management on AMI survival using propensity score and instrumental variable methods. *JAMA*. 2007; 297:278–285. [PubMed: 17227979]
18. Cepeda MS, Boston R, Farrar JT, et al. Comparison of logistic regression versus propensity score when the number of events is low and there are multiple confounders. *Am J Epidemiol*. 2003; 158:280–287. [PubMed: 12882951]
19. Johnston, SC.; Easton, JD. Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial, a randomized, double-blind, multicenter clinical trial. National Library of Medicine (US); Bethesda, MD: 2011. Available at: <http://clinicaltrials.gov/ct2/show/NCT00991029>NLM Identifier: NCT00991029 [Accessed January 16, 2012]

Table 1

Baseline characteristics for clopidogrel loading among the propensity score–matched cohorts

	No loading dose	Loading dose	<i>P</i> value
Age (y), mean (SD)	63 (2.2)	64 (1.8)	.67
Gender, male, %	60.0 (33/55)	58.2 (32/55)	.85
Race/ethnicity, %			.19
White	32.7 (18/55)	20.0 (11/55)	
Black	63.7 (35/55)	80.0 (44/55)	
Asian	1.8 (1/55)	0 (0/55)	
Hispanic	1.8 (1/55)	0 (0/55)	
NIHSS on admission, median, IQR	4 IQR 2,7	4 IQR 2, 9	.67
History of prior stroke, %	45.5 (25/55)	45.5 (25/55)	1.00
History of CAD, %	25.4 (14/55)	14.6 (8/55)	.15
History of systemic bleeding, %	3.6 (2/55)	3.6 (2/55)	1.00
Old hemorrhage on MRI gradient echo, %	16.3 (8/49)	22.6 (12/53)	.42
TOAST classification			.71
Cardioembolic, %	21.8 (12/55)	27.3 (15/55)	
Large artery atherosclerosis, %	32.7 (18/55)	32.7 (18/55)	
Small vessel occlusion, %	25.5 (14/55)	18.2 (10/55)	
Cryptogenic, %			
More than 1 cause	0 (0/55)	1.8 (1/55)	
No cause	16.4 (9/55)	12.7 (7/55)	
Other etiology, %	3.6 (2/55)	7.3 (4/55)	

Abbreviations: IQR, interquartile range; CAD, coronary artery disease; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

Table 2

Bleeding events for clopidogrel loading among the propensity score–matched cohorts

	No loading dose	Loading dose	<i>P</i> value
Any serious bleeding event, %	15.6 (7/45)	14.3 (6/42)	.87
Symptomatic ICH, %	2.1 (1/46)	0 (0/41)	.34
Transfusion of blood products, %	11.1 (6/54)	10.9 (6/55)	.97
Any hemorrhagic transformation, %	12.7 (7/55)	3.6 (2/55)	.08
Systemic bleeding, %	5.4 (3/55)	9.1 (5/55)	.46

Abbreviation: ICH, intracerebral hemorrhage.

Table 3

Odds of having a serious bleeding event following clopidogrel loading when compared with patients who were not given a loading dose of clopidogrel

	OR	95% CI
Full sample, no adjustment	.85	.39-1.85
Full sample, only adjusting for PS	.96	.33-2.83
Full sample, no PS, adjustment for NIHSS, age, admission glucose	.91	.41-2.02
Full sample, adjustment for PS, NIHSS, age, admission glucose	.97	.32-2.93
PS matched, no adjustment	.92	.27-3.13
PS matched, adjusting only for PS	.91	.26-3.14
PS matched, adjusting for age, admission glucose, NIHSS on admission	1.04	.28-3.90
PS matched adjusting for PS, age, admission glucose, NIHSS on admission	1.06	.28-4.04

Abbreviations: CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; PS, propensity score.