Vascular Health and Risk Management

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ORIGINAL RESEARCH

Comparative effect of clopidogrel plus aspirin and aspirin monotherapy on hematological parameters using propensity score matching

This article was published in the following Dove Press journal:
Vascular Health and Risk Management
16 February 2013
Number of times this article has been viewed

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Background: Clopidogrel and aspirin are antiplatelet agents that are recommended to reduce the risk of recurrent stroke and other cardiovascular events. Dual antiplatelet therapy with clopidogrel and aspirin has been shown to increase the risk of hemorrhage, but the effects of the drugs on laboratory parameters have not been well studied in real-world clinical settings. Therefore, we evaluated and compared the effects of combination therapy with clopidogrel plus aspirin and aspirin monotherapy on laboratory parameters.

Methods: We used data from the Nihon University School of Medicine Clinical Data Warehouse obtained between November 2004 and May 2011 to identify cohorts of new users (n = 130) of clopidogrel (75 mg/day) plus aspirin (100 mg/day) and a propensity score matched sample of new users (n = 130) of aspirin alone (100 mg/day). We used a multivariate regression model to compare serum levels of creatinine, aspartate aminotransferase, and alanine aminotransferase, as well as hematological parameters including hemoglobin level, hematocrit, and white blood cell, red blood cell, and platelet counts up to 2 months after the start of administration of the study drugs.

Results: There were no significant differences for any characteristics and baseline laboratory parameters between users of clopidogrel plus aspirin and users of aspirin alone. Reductions in white blood cell and red blood cell counts, hemoglobin levels, and hematocrit in users of clopidogrel plus aspirin were significantly greater than those in users of aspirin alone.

Conclusion: Our findings suggest that adverse hematological effects may be greater with combination clopidogrel plus aspirin therapy than with aspirin monotherapy.

Keywords: clopidogrel, aspirin, laboratory parameter, antiplatelet therapy, propensity score matching

Introduction

Antiplatelet therapy is indicated for secondary prevention in patients with transient ischemic attack or ischemic stroke.[1] The combination of clopidogrel and aspirin has been shown to reduce the risk of ischemic events in patients with myocardial infarction with or without ST segment elevation, and after angioplasty or stenting.[2–5] On the other hand, in the MATCH trial, combination therapy with clopidogrel plus aspirin in patients with a prior stroke or transient ischemic attack showed no significant benefit in reducing major vascular events compared with clopidogrel alone.[6] Furthermore, the CHARISMA trial has shown that the combination of clopidogrel and aspirin was not significantly more effective than aspirin alone in reducing the rate of myocardial infarction, stroke, or death from cardiovascular causes.[7] In addition, some trials have reported that the risk of major and moderate bleeding is increased in patients treated with

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the combination of clopidogrel and aspirin.[2,6–8] Based on these clinical findings, the American Heart Association/American Stroke Association guidelines do not recommend routine combination therapy with aspirin and clopidogrel for patients with ischemic stroke or transient ischemic attack, although this dual antiplatelet therapy may be appropriate for patients with acute coronary syndromes or after vascular stenting.[1] Although these previous clinical studies have examined the side effects of combination therapy using clopidogrel plus aspirin, they have usually focused on the adverse events of antiplatelet agents, and there are few studies focused on the effects of these drugs on laboratory parameters. Therefore, we evaluated and compared the effects of combination therapy with clopidogrel plus aspirin and aspirin monotherapy on laboratory parameters, focusing on hematological parameters including red blood cell, white blood cell, and platelet counts, as well as hemoglobin levels and hematocrit.

Materials and methods

Data source

We obtained the study data from electronic medical records stored in the Nihon University School of Medicine Clinical Data Warehouse, which is a centralized data repository that integrates separate databases, such as an order entry database and a laboratory results database, from the hospital information systems at three hospitals affiliated with the Nihon University School of Medicine, and has been described elsewhere.[9] The prescription database in the Clinical Data Warehouse contains information from approximately 0.5 million patients, with prescribing data linked longitudinally to detailed clinical information, such as patient demographics, diagnosis, and laboratory data. Several epidemiological studies examining the effects of drugs on laboratory parameters using the Nihon University School of Medicine Clinical Data Warehouse have been published.[10–12]

Study population

For this study, we identified Japanese patients aged over 20 years who had been newly treated with clopidogrel 75 mg/day plus aspirin 100 mg/day or aspirin 100 mg/day alone between November 2004 and May 2011. We excluded patients with severe comorbid conditions, ie, increased risk of bleeding, including diagnosis of severe hepatic insufficiency and current peptic ulceration, or history of systemic bleeding, other history of bleeding diathesis or coagulopathy, or a contraindication for aspirin or clopidogrel during the study period. Consequently, we identified 173 new users of clopidogrel plus aspirin and 966 new users of aspirin alone. We then identified new users of clopidogrel plus aspirin (n = 130) and an equal number of new users of aspirin alone (n = 130) using propensity score matching to adjust for differences in baseline covariates between users.

Exposure and outcome

In this study, the index date was defined as the date of first prescription of the study drugs. The baseline (nonexposure) measurement period was defined as the 6 months before the index date in the clopidogrel plus aspirin and aspirin alone cohorts. The exposure (outcome measurement) period was defined as between 2 weeks and 2 months after the start of treatment with clopidogrel plus aspirin or aspirin alone. Blood test data (creatinine, aspartate aminotransferase, and alanine aminotransferase levels) and hematological parameters (red blood cell, white blood cell, and platelet counts, hemoglobin level, and hematocrit) were collected for each individual at the date nearest the index date in the baseline period, and at the date nearest 2 months after the start of treatment in the exposure period. Consequently, the mean (95% confidence interval) exposure of users of clopidogrel plus aspirin and users of aspirin alone was 35.3 (32.9–37.7) days and 38.6 (36.2–41.1) days, respectively. Information on bleeding episodes in patients who were newly diagnosed with intracranial hemorrhage or gastrointestinal bleeding in the exposure period was collected.

Covariates

For each individual, information on patient demographics (age and gender), medical history, current medication, and laboratory results was collected. Medical history included information on cerebrovascular disease (ICD-10 codes I60–I69), ischemic heart disease (I20–I25), other heart disease (I30–I52), liver disease (K70–K77), kidney disease (N00–N19), gout (M10), thyroid gland disorder (E00–E07), hyperlipidemia (E78.0–E78.5), hypertension (I10), and diabetes mellitus (E10–E14), which had been diagnosed prior to the index date. We recorded current medication being used, including antihypertensive agents, steroids, lipid-lowering drugs, insulin, oral antihyperglycemic agents, nonsteroidal anti-inflammatory drugs, proton pump inhibitors, histamine-2 receptor antagonists, other antipeptic ulcer agents, immunosuppressive drugs, diuretics, antiarrhythmic agents, and thyroid drugs, defined as having been received in the 60 days preceding the index date.

Statistical analysis

To reduce bias as a result of balancing covariates between settings, we used propensity score matching, which is

becoming more widely used in cardiovascular research.[10,13] The cohorts of users of clopidogrel plus aspirin and users of aspirin alone were matched by propensity score using a nearest neighbor-matching algorithm with a "greedy" heuristic, with matching occurring if the difference in the logits of the propensity scores was less than 0.2 times the standard deviation of the scores.[14,15] To generate the propensity score, we used covariates including age, gender, comorbid diseases (cerebrovascular disease, ischemic heart disease, other heart disease, liver disease, kidney disease, gout, thyroid gland disorder, hyperlipidemia, hypertension, and diabetes mellitus), and previous drug therapy (including antihypertensive agents, steroids, lipid-lowering drugs, oral antihyperglycemic agents, nonsteroidal anti-inflammatory drugs, proton pump inhibitors, histamine-2 receptor antagonists, other antipeptic ulcer agents, immunosuppressive drugs, antiarrhythmic drugs, and chemotherapeutic drugs), as listed in Table 1. After propensity score matching, we compared the prevalence of all baseline covariates using the *t*-test for continuous variables and the Chi-squared test for categorical data. We also used the *t*-test to compare the mean values for laboratory parameters at baseline between users of clopidogrel plus aspirin and users of aspirin alone. Univariate and multivariate generalized linear models were used to compare the mean change from the baseline value with the exposure value between users of clopidogrel plus aspirin and users of aspirin alone. In the adjusted model, with age and gender forced into the model, the remaining covariates were selected using a backward stepwise elimination method ($P < 0.10$). All reported P values <0.05 were considered to indicate statistical significance. All statistical analyses were performed using SAS software version 9.2 (SAS Institute Inc, Cary, NC).

Results

The study included 130 patients newly treated with clopidogrel plus aspirin and 130 matched patients newly treated with aspirin alone. Table 1 shows the characteristics of the patients after propensity score matching. There were no statistically significant differences in any covariates between users of clopidogrel plus aspirin and users of aspirin alone; their mean age was 65.8 years and 66.9 years, respectively, and 23.1% and 23.9% of users of clopidogrel plus aspirin and users of aspirin alone were women. More than three quarters of each cohort had ischemic heart disease, hyperlipidemia, or diabetes mellitus, suggesting an increased risk of cardiovascular disease. With regard to current medications, about two fifths took one or more antihypertensive agent, one third took a calcium channel blocker, and one fifth took an angiotensin II receptor blocker. About one fifth of each cohort took a lipid-lowering drug, and one fifth took a hypoglycemic drug. Table 2 shows the mean values for laboratory parameters at baseline. There were no significant differences in any of the tests investigated between users of clopidogrel plus aspirin and users of aspirin alone.

Table 3 shows the mean changes in laboratory parameters during the exposure period compared with baseline. In users of clopidogrel plus aspirin, the reductions in white and red blood cell counts, hemoglobin level, and hematocrit were significantly greater than those in users of aspirin alone before and after adjustment for the covariates. The mean changes in creatinine, aspartate transaminase, and alanine aminotransferase levels, as well as platelet count, were not significant in users of clopidogrel plus aspirin in comparison with levels in users of aspirin alone.

Table 4 shows the prevalence of patients who had hemorrhagic events during the exposure period. Gastrointestinal bleeding and intracranial hemorrhage occurred more frequently in users of clopidogrel plus aspirin than in users of aspirin alone, although the numbers of patients with adverse events were small.

Discussion

In this study, we evaluated and compared the effects of combination therapy of clopidogrel plus aspirin and aspirin monotherapy on hematological parameters, including creatinine, aspartate transaminase, alanine aminotransferase, hemoglobin level, hematocrit, and white blood cell, red blood cell, and platelet counts during a short-term administration period of up to 2 months. We found that the reductions in white blood cell and red blood cell counts, hemoglobin level, and hematocrit in users of clopidogrel plus aspirin were significantly greater than those in users of aspirin alone. These results suggest that adverse hematological effects are greater with combination therapy of clopidogrel plus aspirin than with aspirin monotherapy.

A variety of adverse hematological reactions, including leukopenia, agranulocytosis, and thrombocytopenia, have been reported in patients receiving clopidogrel or aspirin.[16–19] In the CAPRIE trial, the numbers of patients with a significant reduction in neutrophils were 0.10% and 0.17% in the clopidogrel and aspirin groups, respectively.[16] Our findings support those of previous studies suggesting that use of these antiplatelet agents may be associated with leukopenia.

Table 1 Baseline characteristics after propensity score matching

Characteristics	Clopidogrel plus aspirin (n = 130)	Aspirin alone (n = 130)	*P* value
Age (mean ± SE)	65.9 ± 1.0	67.0 ± 1.0	0.8928
Women	30 (23.08%)	31 (23.85%)	0.8836
Age over 75 years	32 (24.62%)	35 (26.92%)	0.6705
Medical history			
Cerebrovascular disease	35 (26.92%)	39 (30%)	0.5825
Ischemic heart disease	110 (84.62%)	108 (83.08%)	0.7361
Other heart disease	84 (64.62%)	81 (62.31%)	0.6992
Liver disease	36 (27.69%)	38 (29.23%)	0.7834
Kidney disease	57 (43.85%)	60 (46.15%)	0.7084
Hypertension	78 (60%)	79 (60.77%)	0.8991
Thyroid disorder	37 (28.46%)	37 (28.46%)	1
Diabetes mellitus	101 (77.69%)	106 (81.54%)	0.4415
Hyperlipidemia	118 (90.77%)	115 (88.46%)	0.5419
Current medications			
Insulin	3 (2.31%)	5 (3.85%)	0.4726
Oral hypoglycemic drugs	23 (17.69%)	28 (21.54%)	0.4349
Lipid-lowering drugs	31 (23.85%)	29 (22.31%)	0.7685
Antihypertensive drugs	54 (41.54%)	56 (43.08%)	0.8018
ARB	28 (21.54%)	36 (27.69%)	0.2494
ACEI	5 (3.85%)	4 (3.08%)	0.7344
Beta-blockers	7 (5.38%)	6 (4.62%)	0.776
CCB	41 (31.54%)	39 (30%)	0.7881
Thiazide diuretics	12 (9.23%)	16 (12.31%)	0.4236
Others	16 (12.31%)	15 (11.54%)	0.8482
NSAIDs	11 (8.46%)	10 (7.69%)	0.82
Steroids	4 (3.08%)	3 (2.31%)	0.7016
H2 blockers	18 (13.85%)	23 (17.69%)	0.3949
Proton pump inhibitors	14 (10.77%)	17 (13.08%)	0.5659
Antiepileptic drugs	4 (3.08%)	3 (2.31%)	0.7016
Immunosuppressive drugs	0 (0%)	0 (0%)	–
Diuretics	11 (8.46%)	14 (10.77%)	0.528
Thyroid drugs	1 (0.77%)	0 (0%)	0.3164
Antiarrhythmic drugs	13 (10%)	16 (12.31%)	0.5545

Note: Data are numbers of individuals (%) unless otherwise stated.
Abbreviations: ARB, angiotensin II receptor blockers; ACEI, angiotensin-converting enzyme inhibitors; CCB, calcium channel blockers; NSAID, nonsteroidal anti-inflammatory drugs; H2 blocker, histamine-2 receptor antagonists.

Furthermore, our findings suggest the possibility that addition of clopidogrel to aspirin may enhance the adverse effect of aspirin alone on white blood cell count, although it is not clear whether or not the effects of these antiplatelet agents are dose-dependent. Our study may help physicians to make decisions on drug selection, especially when treating patients with a borderline low white blood cell count.

In this study, we used propensity score matching to balance the population of users of covariate, a potential confounding variable, between users of clopidogrel plus aspirin and users of aspirin alone, and found significant adverse effects on red blood cell count, hemoglobin level, and hematocrit in users of clopidogrel plus aspirin compared with users of aspirin alone. The nature of antiplatelet therapy involves an inherent risk of bleeding complications. Some trials have reported that addition of aspirin to clopidogrel increases the risk of hemorrhage.[2,6–8] Supporting this, our study showed that hemorrhagic events occurred more frequently in patients receiving clopidogrel plus aspirin than in patients receiving aspirin alone (Table 4). These patients may have impacted on our hematological results. Therefore, we reanalyzed the data without patients who had hemorrhagic events, and found that the reductions in red blood cell and white blood cell counts in users of clopidogrel plus aspirin remained significant in comparison with those in users of aspirin alone (data not shown). Our findings, combined with previous reports, suggest that regular checks of hematological parameters should be performed, especially within the 2 months after initiating therapy.

Table 2 Baseline laboratory parameters of studied patients

Laboratory test	Clopidogrel plus aspirin (n = 130)	Aspirin alone (n = 130)	*P* value
Creatinine (mg/dL)	1.15 ± 1.37	1.26 ± 1.54	0.5401
ALT (U/L)	30.94 ± 36.97	30.94 ± 73.31	1
AST (U/L)	41.56 ± 68.99	30.49 ± 38.45	0.1113
WBC (10^3/μL)	7.58 ± 3.25	7.22 ± 2.9	0.3516
RBC (10^6/μL)	4.15 ± 0.75	4.01 ± 0.73	0.125
Platelets (10^3/μL)	220.36 ± 71.53	239.32 ± 94.56	0.0694
Hemoglobin (g/dL)	13.05 ± 2.38	12.68 ± 2.32	0.213
Hematocrit (%)	38.57 ± 6.90	37.59 ± 6.64	0.244

Note: Data other than *P* values are presented as mean ± standard deviation.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; WBC, white blood cell count; RBC, red blood cell count.

Our study has several limitations. First, the retrospective design with nonrandomized assignment involved inherent issues of selection bias and confounding. We used rigorous statistical methods to balance potential confounding variables between users of clopidogrel plus aspirin and users of aspirin alone, including propensity score matching and a multivariate regression model. However, their ability to control for differences was limited to variables that were available and measurable. Second, there is also the possibility of inaccuracy of information in the database (eg, misclassification of exposure and outcome, ie, ascertainment bias). Prescription claims data and medical records are considered by many to be the gold standard for measuring drug exposure and for capturing intermediate and final outcomes, respectively.[20] However, the Nihon University School of Medicine Clinical Data Warehouse used in this study may combine the best of both worlds by linking a prescription database to detailed medical information, and is suitable for pharmacoepidemiological research. Third, this study was undertaken to compare the effects of clopidogrel plus aspirin and aspirin alone on laboratory test results in a Japanese population, so the cohorts identified for the study included only Japanese patients. Therefore, it cannot be concluded that the present findings can be extended to people of other races, such as Caucasians. The findings of our study, based on a nonrandomized design, call for further studies, such as similar analyses of larger international databases or randomized clinical trials for confirmation.

Table 3 Mean changes in laboratory parameters values during exposure period from baseline

Laboratory test	Unadjusted			Adjusted		
	Mean	(95% CI)	*P* value	Mean	(95% CI)	*P* value
ΔCreatinine (mg/dL)						
Clopidogrel plus aspirin (n = 130)	0.0211	(–0.0650, 0.1072)	0.2498	0.0056	(–0.1340, 0.1451)	0.3538
Aspirin alone (n = 130)	–0.0502	(–0.1363, 0.0359)		–0.0528	(–0.1850, 0.0795)	
ΔALT (U/L)						
Clopidogrel plus aspirin (n = 130)	0.2308	(–13.2222, 13.6837)	0.3167	4.3476	(–48.6200, 57.3152)	0.2465
Aspirin alone (n = 130)	–9.4615	(–22.9145, 3.9914)		–7.1947	(–59.9928, 45.6034)	
ΔAST (U/L)						
Clopidogrel plus aspirin (n = 130)	–13.7385	(–24.5417, –2.9353)	0.3924	–10.5413	(–63.3019, 42.2193)	0.4593
Aspirin alone (n = 130)	–7.0923	(–17.8955, 3.7109)		–3.7961	(–55.3231, 47.7310)	
ΔWBC (10^3/μL)						
Clopidogrel plus aspirin (n = 130)	–1.6069	(–2.1008, –1.113)	0.0084	–1.602	(–2.1448, –1.0591)	0.0101
Aspirin alone (n = 130)	–0.6646	(–1.1585, –0.1707)		–0.6799	(–1.2230, –0.1368)	
ΔRBC (10^6/μL)						
Clopidogrel plus aspirin (n = 130)	–0.098	(–0.1799, –0.0161)	0.0117	–0.0385	(–0.1295, 0.0525)	0.0030
Aspirin alone (n = 130)	0.0513	(–0.0306, 0.1332)		0.1365	(0.0405, 0.2324)	
ΔPLT (10^3/μL)						
Clopidogrel plus aspirin (n = 130)	0.8	(–11.8278, 13.4278)	0.1864	–3.3383	(–59.7804, 53.1037)	0.2259
Aspirin alone (n = 130)	–11.2154	(–23.8432, 1.4124)		–14.5070	(–71.8512, 42.8371)	
ΔHemoglobin (g/dL)						
Clopidogrel plus aspirin (n = 130)	–0.2977	(–0.5569, –0.0385)	0.0115	–0.3143	(–0.8081, 0.1795)	0.0020
Aspirin alone (n = 130)	0.1762	(–0.0831, 0.4354)		0.2587	(–0.2273, 0.7447)	
ΔHematocrit (%)						
Clopidogrel plus aspirin (n = 130)	–0.9092	(–1.6655, –0.1530)	0.0124	–0.2871	(–1.1229, 0.5487)	0.0030
Aspirin alone (n = 130)	0.4585	(–0.2978, 1.2147)		1.3227	(0.4410, 2.2044)	

Note: Δ indicates mean change in laboratory test value between baseline and exposure period.
Abbreviations: CI, confidence interval; ALT, alanine aminotransferase; AST, asparate aminotransferase; WBC, white blood cell count; RBC, red blood cell count; PLT, platelet count.

Table 4 Prevalence of hemorrhagic events

Hemorrhagic event	Clopidogrel plus aspirin (n = 130)	Aspirin alone (n = 130)
Intracranial hemorrhage	3 (2.3%)	1 (0.8%)
Gastrointestinal bleeding	5 (3.8%)	0 (0%)

Note: Data are numbers of individuals (%).

Conclusion

Our study, conducted in a real-world setting, showed that reductions in white and red blood cell counts, hemoglobin level, and hematocrit in users of clopidogrel plus aspirin were significantly greater than those in users of aspirin alone, suggesting that adverse hematological effects are greater with combination therapy of clopidogrel plus aspirin than with aspirin monotherapy. Our findings support the experience noted in clinical practice that use of dual antiplatelet therapy requires regular checks of hematological parameters.

Disclosure

The authors declare that they have no competing interests in this work.

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