British Journal of Medicine & Medical Research
5(5): 642-650, 2015, Article no.BJMMR.2015.070
ISSN: 2231-0614

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Unexpected Discontinuation of Dual Antiplatelet Therapy within 14 Days after Percutaneous Coronary Intervention: A Single-center Case Series

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Authors' contributions

This work was equally carried out in collaboration between authors TK and SH. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJMMR/2015/12927
Editor(s):
(1) Gaetano Santulli, College of Physicians and Surgeons Columbia University Medical Center New York, NY, USA.
Reviewers:
(1) Marina Moguilevitch, Department of Anesthesiology, Montefiore Medical Center, Bronx, USA.
(2) David Gruenebaum, Department of Medicine, Michigan State University, USA.
(3) Anonymous, University of Ferrara, Italy.
(4) Anonymous, Dong-A University, Korea.
Complete Peer review History: http://www.sciencedomain.org/review-history.php?iid=672&id=12&aid=6280

Case Study

Received 23rd July 2014
Accepted 12th September 2014
Published 30th September 2014

ABSTRACT

Objectives: To provide a descriptive case-series of patients who unexpectedly discontinued dual antiplatelet therapy (DAPT) within 14 days after percutaneous coronary intervention (PCI) (group A), and those who had taken measures for bleeding risk reduction before PCI (group B).
Study Design: Case study.
Place and Duration of Study: Cardiovascular Center, Kitano Hospital, the Tazuke Kofukai Medical Research Institute, between 2009 and 2011.
Methods and Results: We retrospectively reviewed 346 patientsundergoing PCI in our hospital. In group A (n=12, 3.46%), 10 patients underwent emergent PCI including 3 cases of cardiopulmonary arrest. The procedures were 8 cases of bare metal stent implantation, 2 cases of drug-eluting stent (DES) implantation, and 2 cases of balloon angioplasty. The reasons for discontinuation included 6 cases of bleeding, out of which 4 cases involved pulmonary bleeding, and 3 involved sequential operation. The mean time of DAPT cessation was 3.3 days. The mortality rate of patients with pulmonary bleeding was 75%. In group B (n=9, 2.60%), 4 cases were emergent PCI and 5 were

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scheduled. Reasons for taking bleeding risk reduction measures included past history of bleeding, cancer, and poor adherence. The methods of bleeding risk reduction included avoidance of DES and the use of cilostazol, which resulted in noserious bleeding or thrombosis occurring.
Conclusions: A descriptive case-series of patients who unexpectedly discontinued DAPT within 14 days and those who had taken bleeding risk reduction measures before PCI was provided. Our results imply that careful planning regarding the antiplatelet therapy and risk assessment for bleeding, including pulmonary bleeding, are warranted for patients undergoing PCI.

Keywords: Dual antiplatelet therapy; discontinuation; percutaneous coronary intervention; cilostazol.

1. INTRODUCTION

Heart disease is the leading cause of death both in developed world and in developing regions [1,2]. In particular, ischemic heart disease accounts for 1.4 million deaths in the developed countries and 5.7 million deaths in developing countries [3]. In patients undergoing invasive treatment for acute coronary syndromes, bleeding is a serious complication, and is associated with a markedly worse prognosis and increased 30-day mortality [4]. Although highly efficient, antithrombotic therapy is associated with an increased risk of bleeding. In terms of oral antiplatelet therapy, dual antiplatelet therapy (DAPT) is generally recommended by various guidelines for at least six months to one year post-procedure depending on the specific situation and stents used [5-7]. A previous report investigating the prevalence, predictors, and long-term prognosis of premature discontinuation of oral antiplatelet therapy after drug eluting stent (DES) implantation [8] showed that premature discontinuation of antiplatelet therapy is relatively common, especially within the first year after DES implantation, and this was strongly associated with an increased risk of cardiovascular events, including ST elevation and death. In addition, DAPT interruption within the first month (> 1day post-procedure) was found to be associated with a high risk of adverse outcomes in a pooled population of patients undergoing a RESOLUTE zotarolimus-eluting stent implantation [9]. However, little is currently known regarding the effects of unexpected discontinuation of dual antiplatelet therapy within a short duration (i.e. 14 days) after percutaneous coronary intervention (PCI). Since most of the adverse outcomes including stent thrombosis and acute closure, are known to generally occur within 15 days of PCI [10-12], we retrospectively analyzed the clinical characteristics associated with unexpected discontinuation of dual antiplatelet therapy within 14 days after PCI in the present study. In addition, patients who had taken measures to avoid bleeding before undergoing PCI were also characterized. The purpose of this study was to provide a descriptive case-series regarding the characteristics and different outcomes of these patients.

2. METHODS

2.1 Study Population

We retrospectively extracted all subjects who unexpectedly discontinued dual antiplatelet therapy within 14 days after PCI (group A) and all subjects who had taken measures to avoid bleeding before undergoing PCI (group B) from all patients (n=346) who underwent scheduled or emergent PCI between January 2009 and December 2011 in Kitano hospital. This retrospective study protocol was approved by the ethics committee in our institution.

2.2 Pre-PCI and PCI Protocols

DAPT was administered at a dose of 81 mg of aspirin and 75 mg of clopidogrel, which was started at least three days before the procedure. When urgent PCI was planned and antiplatelet therapy had not been administered, a loading dose of 300mg of clopidogrel and 162 mg of aspirin was administered before the urgent PCI, followed by the standard dose from the day after PCI. PCI was performed according to the guidelines of the Japanese Society of Cardiology [7]. Eight thousand units of heparin sodium were injected via an arterial sheath before the PCI procedure. During PCI, the activated clotting time was monitored and maintained around 250 s by additional administration of heparin according to guidelines [7]. In group B, the methods for reducing the risk of bleeding were avoidance of DES and the use of 200mg of cilostazol added to 81 mg of aspirin, or balloon dilatation (plain old balloon angioplasty; POBA) with 81 mg of aspirin and continuous infusion of heparin three days after PCI.

2.3 Data Collection and Definition

Medical records were reviewed for symptoms, coronary angiography, diagnoses, the reasons for discontinuation of DAPT, and the methods used to avoid bleeding during and after PCI. Bleeding events were defined as moderate or severe bleeding according to the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries classification [13]. Gastrointestinal tract bleeding was defined as 1) vomiting blood, 2) the suction of blood from a feeding tube, or 3) bloody stool, all of which caused a hemodynamic collapse and/or required blood transfusion. Pulmonary bleeding was defined as 1) massive hemoptysis and 2) the suction of blood from the intubation tube, both of which required intubation or intensive respiratory care, such as positive pressure ventilation and supplemental oxygen. Early stent thrombosis or closure was defined as either acute (<24 hours) or early (1-30 days) events. The treatment outcomes were assessed at discharge from the hospital.

2.4 Statistics

Logistic analyses were used to assess the risk factors associated with mortality in group A. Differences between the groups were analyzed by ANOVA followed by post hoc comparisons using the Bonferroni test. Categorical data were analyzed using Chi-square test. In all tests, *P* values< 0.05 were considered significant.

3. RESULTS

The patient characteristics in group A (n=12, 3.46% of all cases) are shown in Table 1. The mean age was 69.6 years and 66% of the patients were men. Ten cases were emergent PCI, including 3 cases of cardiopulmonary arrest on arrival, while two were elective. The stents implanted were bare metal stents (BMS) and DES in 6 and 2 cases, respectively, whereas plain old ballooning angioplasty was conducted in 4 cases. The reasons for discontinuation were 2 cases of gastrointestinal tract bleeding, 2 cases of pulmonary bleeding, 2 cases of both gastrointestinal tract and pulmonary bleeding,3 cases of sequential operation, 2 cases of acute worsening of congestive heart failure unable to receive oral DAPT, and one case of sudden death due to arrhythmia. The mean duration of antiplatelet therapy cessation was 3.3 days. The mortality rate of patients with pulmonary bleeding was 75% (3/4 cases), with one patient still alive at the latest follow-up after receiving long-term mechanical ventilation assistance. Upon discontinuation, aspirin alone was administered when the situation was controlled. After confirmation of bleeding cessation or recovery from the surgery or specific situation, the second antiplatelet agent was also restarted. Acute or early stent thrombosis or closure was not observed in the surviving patients after discontinuation. When surgical cases and cases with worsening of CHF were excluded, emergency setting and pulmonary bleeding were found to be significant risk factors for death in patients in group A as determined by the logistic analyses (Table 2).

Nine patients (2.60%) had taken measures to avoid bleeding during and after PCI. In this group (group B: Table 3), 4 cases were emergent PCI and 5 cases were scheduled. The reasons for taking preoperative measures to avoid bleeding included a history of gastrointestinal bleeding (4 cases), pulmonary bleeding (1 case), pulmonary cancer (1 case), simultaneous onset of cerebral infarction (1 case), anemia due to myelodysplastic syndrome (1 case), and adherence of the drug (1 case). The methods for reducing the risk of bleeding were avoidance of DES in 6 cases, and the use of POBA rather than stents in 3 cases. Aspirin and three-day infusion of heparin was administered in 2 of the 3 cases of POBA, while all other patients were treated by the addition of 200 mg of cilostazol to 81 mg of aspirin. All patients in group B avoided not only serious bleeding events but also acute and early stent thrombosis or closure. In comparison with group A, there were no significant differences in terms of the estimated glomerular filtration rate (eGFR), hemoglobin, and platelet levels; whereas the prevalence of emergency procedure was lower in group B (Table 4).

4. DISCUSSION

We here reported on the clinical characteristics and outcomes in patients who unexpectedly discontinued dual antiplatelet therapy within 14 days after PCI. We found that many of these cases were emergency PCI, and that DAPT was stopped in half of the cases due to bleeding, which was associated with a high mortality rate. We also provided a case-series of patients who had taken preoperative measures to reduce the risk of bleeding during and after PCI, mainly due to a history of bleeding, and we found that these measures successfully resulted in avoidance of bleeding events during and after PCI.

Table 1. Demographic and clinical characteristis of patients discontinuating dual antiplatelet therapy (DAPT) within 14 days after percuatneous coronary intervention (PCI) (n=12)

No	Age	Sex	Past history	Diagnosis	Emergency	PCI	Reason for discontinuation	DAPT duration (days)	Outcomes
1	69	M	Gastric cancer (stageIV) SSc, IP, PH	AMI	Yes	BMS	GI tract bleeding	1[a)]	Dead
2	77	M	Surgery for esophageal cancer	uAP	No	DES	Pulmonary bleeding	7	Alive
3	81	M	Cerebral infarction, DM, HTN, SSS	AP	No	DES	GI tract bleeding	13	Alive
4	77	M	6 days after surgery for lung cancer	AMI	Yes	POBA	Pulmonary bleeding	0[b)]	Dead
5	58	F	Aortitis syndrome	uAP, aortic regurgitation	Yes	BMS	Surgery for aortic regurgitation	4	Dead
6	65	F	None	AMI	Yes	BMS	Cardiac tamponade	6	Alive
7	77	M	Ischemic heart disease	uAP	Yes	POBA	Aortic dissection	1[a)]	Alive
8	91	F	None	AMI	Yes	BMS	Discontinuation of oral intake due to worsening of CHF	1[a)]	Dead
9	90	F	OMI, AP, HTN	AMI	Yes	POBA	Discontinuation of oral intake due to worsening of CHF	3	Alive
10	49	M	OMI	AMI	Yes	BMS	Sudden death	1[a)]	Dead
11	46	M	None	AMI	Yes	BMS	Pulmonary and GI bleeding	1[a)]	Dead
12	55	M	None	AMI with aortic dissection	Yes	POBA	Pulmonary and GI bleeding	1[a)]	Dead

[a)] The day after of PCI. [b)] On the day of PCI.AMI; acute myocardial infarction, BMS; bare metal stent, GI; gastrointestinal, SSc; systemic sclerosis, IP; interstitial pulmonary fibrosis, PH; pulmonary hypertention, AP; angina pectoris, uAP; unstable AP, DES; drug eluting stent, DM; diabetes mellitus, HTN; hypertension, SSS; sick sinus syndrome, POBA; plain old baloon angioplasty, OMI; old myocardial infarction, CHF; congestive heart failure

Table 2. Logistic regression analyses for mortality in patients in group A

Risk for mortality	Likelyfood ratio	P value (Prob>ChiSq)
Pulmonary bleeding	3.819	0.047
Gastrointestinal bleeding	2.772	0.095
Emergency procedure	6.591	0.012

4.1 Risk Assessment for Bleeding

The prevalence of pulmonary bleeding during antiplatelet therapy is reported to be relatively low (0.5-0.9%). However, the mortality rate associated with pulmonary bleeding is reportedly very high (29-50%) [14,15], which is consistent with our findings in group A (Table 1). The risk factors of pulmonary bleeding include chronic obstructive pulmonary disease, interstitial fibrosis, pulmonary hypertension, and congestive heart failure [16]. In addition, advanced age, female sex, anemia before antiplatelet therapy, renal dysfunction (eGFR< 60ml/min/1.73m^2), the use of infusion of Glycoprotein IIb/IIIa inhibitors and intra-aortic balloon pumping have been reported to be risk factors of pulmonary bleeding [17]. Our data suggest that it is important to assess the risk factors for bleeding, both of the lung and gastrointestinal tract, and that, whenever possible, preoperative measures to reduce the risk of bleeding during and after PCI should be taken in high risk patients. In this study, we were unable to compare groups A and B to other patients who underwent PCI in our hospital. Instead, the focus of our study was to compare patients for whom measures were taken to reduce the risk of bleeding before PCI (group B) to patients who unexpectedly discontinued DAPT treatment (group A). The prevalence of elective procedures was higher in group B; and although there were no statistical differences, the levels of hemoglobin and eGFR tended to be lower in group B. Although these results need to be confirmed in future large-scale studies, these factors may help in the risk stratification for scheduled PCI.

4.2 Unexpected Discontinuation of Dual Antiplatelet Therapy

Although the optimal duration of DAPT after DES implantation has not been yet fully elucidated, the incidence of late and very late stent thrombosis were very low in the early trials of sirolimus-eluting stents [18,19]. The 2011American College of Cardiology/American Heart Association guidelines recommend 12 months of DAPT after stent implantation [5]. In the 2012 European Society of Cardiology guidelines, a 9–12-month duration of DAPT is recommended, with strict minimum durations of one month for patients who receive a BMS and six months for those who receive a DES [6]. Of note, the effects of premature discontinuation of DAPT have been recently called to attention. Results from the patterns of non-adherence to anti-platelet regimens in stented patients (PARIS) registry [8] showed that the incidences of discontinuation recommended by physicians and disruption due to bleeding or noncompliance were 57.3% and 14.4%, respectively, at 2 years of follow-up. Interestingly, patients with disruption had more major cardiac events than patients still receiving dual antiplatelet therapy, especially when the treatment was disrupted in the first 30 days; within 7 days and 8-30 days, the adjusted hazard ratios were 7.04 and 2.17, respectively [8]. In addition, DAPT interruption within 1 month (> 1day) of stent implantation has been demonstrated to be associated with a high risk of adverse outcomes (3.6% of all long DAPT interruptions) in a pooled population of patients receiving a RESOLUTE zotarolimus-eluting stent [9]. In the present study, unexpected discontinuation of DAPT within 14 days after PCI was found to be associated with a high mortality rate, although we were unable to determine whether the unexpected discontinuation or the consequences of the severity of the diseasewas the cause of the high mortality. DES implantation leads to delay re-endothelialization and subsequent vascular healing [20-23]. Using microRNA for the prevention of restenosis and the complete re-endothelialization and the preservation for endothelial function has reported to be aninnovative therapeutic approach after PCI [24].

4.3 Bleeding Risk Reduction

One of the strategies for the preparation in case of serious bleeding included the use of bare metal stents and/or cilostazol added to aspirin, owing toits rapid metabolism [25]. Cilostazol is a selective inhibitor of 3-type phosphodiesterase (PDE3) and an inhibitor of platelet aggregation, which is mediated by increasing levels of cyclic adenosine monophosphate. The apparent elimination half-life of cilostazol is approximately 11 hours, and its effects completely disappear relatively quickly, around 48 hours [25]; as compared to after 5-7 days in the case of aspirin

Table 3. Demographic and clinical characteristics of patients for whom measures were taken to reduce the risk of bleeding before PCI (group B; n=9)

No	Age	Sex	Past history	Diagnosis	Emergency	PCI	Antiplatelet therapy	Risk factors for bleeding	eGFR (ml/min/1.73m^2)	Hb (g/dl)
1	86	M	OMI	AP	No	BMS	Aspirin+cilostazol	Active gastric ulcer that required bloodtransfusion	55	10.0
2	77	M	OMI, Af, HTN	OMI	No	POBA	Heparin	Diverticular hemorrhage of the large intestine	56	7.3
3	83	M	None	AP	No	POBA	Aspirin+cilostazol	Hemoptysis due to bronchiectasis	56	10.9
4	76	F	None	AP, cAVB	No	BMS	Aspirin+cilostazol	Recent cerebral infarction	74	12.1
5	75	M	HTN	RMI	Yes	POBA	Aspirin	GI tract bleeding	90	14.2
6	75	M	None	AMI	Yes	BMS	Aspirin+cilostazol	GI tract bleeding	44	8.5
7	77	F	None	AMI	Yes	BMS	Aspirin+cilostazol	Poor adherence	10	8.9
8	80	M	None	uAP	Yes	BMS	Aspirin+cilostazol	MDS with anemia	43	6.8
9	59	M	None	uAP	Yes	BMS	Aspirin+cilostazol	Renal and lung cancer	67	15.1

Af; atrial fibrillation, OMI; old myocardial infarction, HTN, hypertension, cAVB; complete AV block, RMI; recent myocardial infarction, AMI; acute myocardial infarction, AP; angina pectoris, uAP; unstable angina pectoris, BMS; bare metal stent, POBA; plain old balloon angioplasty, GI; gastrointestinal, MDS; myelodysplastic syndrome, eGFR; estimated glomerular filtration rate, Hb; hemoglobin

Table 4. Comparisons between the two groups

Characteristics	Group A	Group B	P value
Mortality (%)	58.3 %	0 %	0.002
Emergency/ Elective (%)	83.3%/16.7%	36.3%/63.4%	0.021
Female (%)	33.3%	27.2%	0.752
Age (y.o., mean±SEM)	69 ±3.5	75.8±3.6	0.230
Hemoglobin (g/dL, mean±SEM)	12.3±0.9	10.7±0.7	0.190
Platelet (/μl, mean±SEM)	14.1±3.1	17.4±2.1	0.395
eGFR (mL/min/1.73m^2, mean±SEM)	64.7±11.5	54.7±6.9	0.468

and clopidogrel which work by inducing irreversible blockade of the formation of thromboxane A2 in platelets and irreversible inhibition of the adenosine diphosphate chemoreceptors on the platelet cell membranes, respectively.

Previous studies have shown that cilostazol possesses pleiotropic effects, such as inhibition of neointimal hyperplasia and that it appears to be safe, with no significant increase in the risk of stent thrombosis or bleeding observed, when used together with aspirin for antiplatelet therapy for bare metal stents [26,27]. Conversely, one randomized comparison of 622 patients found that the rate of subacute thrombosis was significantly higher in the cilostazol plus aspirin group compared to in the ticlopidine plus aspirin group (2% vs 0.3%, p=0.02) [28]. In the era of second- and third- generation DES and drug-eluting balloons, the appropriateness of these strategies should be elucidated by large randomized clinical trials for the use in patients at very high risk of intra- or postoperative bleeding.

5. CONCLUSION

We presented a case-series, in which unexpected discontinuation of DAPT within 14 days after PCI was found to associate with poor outcomes, especially secondary to pulmonary bleeding. Based on these results, we conclude that careful planning of antiplatelet therapy and the choice of stent need to be considered while being mindful of the risk of bleeding when PCI is being performed. Thus it is important not just because of the risk of early thrombosis associated with discontinuation, but also because of the exceedingly high mortality resulting from bleeding complications even if the agents are discontinued. Large-scale prospective clinical trials and retrospective analyses are needed to confirm our results and to elucidate the risks of unexpected discontinuation of dual antiplatelet therapy within a very short duration (i.e. 14 days) after PCI and to clarify the risk reduction strategies for bleeding.

6. STUDY LIMITATION

This study was retrospectively analyzed from a single hospital and from a relatively small sample size. Since the purpose of this study was to provide a descriptive case-series, statistical analyses of the usefulness of the various methods for reducing the risk of bleeding was not performed. Lastly, the choice of DAPT as a pre-PCI treatment was dependent on the risk assessment of each cardiologist, and not according to standardized risk stratification or scoring methods.

CONSENT

Not applicable for the retrospective case-series in this cohort study approved by the Institutional Review Board in our hospital.

ETHICAL APPROVAL

This retrospective study protocol was approved by the ethics committee in our institution.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=672&id=12&aid=6280