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Bridging Therapy with Aspirin plus Cilostazol for Periprocedural Management of Antiplatelet Therapy in Patients Undergoing Non-Cardiac Surgery after Drug Eluting Stents Implantation

Cardiology

KEYWORDS: antiplatelet drugs; aspirin; cilostazol; clopidogrel; drug-eluting stents; surgery

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ABSTRACT

Aim: The objectives were to study the outcomes of use of aspirin and cilostazol as bridging therapy for periprocedural management of antiplatelet therapy in patients undergoing non-cardiac surgery within one year after drug eluting stents implantation. **Materials and Methods:** This was a single-centered, retrospective study conducted between September 2013 to March 2016. Nine patients were included in this study. The patients who had undergone non-cardiac surgery with risk of bleeding were given aspirin and cilostazol with discontinuation of clopidogrel prior to procedure. The occurrence of bleeding or any major adverse cardiac events up to 30 days after non-cardiac surgery were observed. **Results:** Of 9 patients, 6 were males. Age range was between 48 and 73 years. There was no occurrence of stent thrombosis, nor were any death or acute coronary syndrome. Only two cases of minor bleeding were observed, but without the need for blood transfusion. **Conclusion:** In cases with high risk for bleeding, bridging therapy with aspirin plus cilostazol for periprocedural management of antiplatelet therapy is associated with low risk of stent thrombosis, however, larger studies would further confirm its efficacy.

Introduction

Stent thrombosis (ST) is one of the dreadful complications after percutaneous coronary intervention. The progressive platelet activation and aggregation results in thrombus formation(Abualsaud & Eisenberg, 2010). Dual antiplatelet therapy (DAPT) with aspirin and clopidogrel is recommended for at least one year after drug eluting stent (DES) implantation and for at least 4 weeks after bare metal stent implantation to prevent stent thrombosis(Mayor, 2006; Silber et al., 2005; Smith et al., 2006). Literature suggests that about 5% of patients require a non-cardiac surgery indication within one year of stent implantation(Marcos, Da Fonseca, & Hofma, 2011). Discontinuation of all antiplatelet agents escalates the relative risk of ST about 90 times(Iakovou et al., 2005). However, the continuation of DAPT during non-cardiac surgery ensues the risk of bleeding. Thus, periprocedural management of antiplatelet therapy in this subset is complicated and requires keen monitoring. On discontinuation of clopidogrel, platelets return to the adequate function after about 5 days(Harder, Klinkhardt, & Alvarez, 2004; Weber et al., 2001). Thus, discontinuation of clopidogrel 5 days prior procedure is recommended by American college of cardiology and American Heart association in patients with high risk of bleeding(Albaladejo, Marret, Piriou, & Samama, 2006; Silber et al., 2005; Smith et al., 2006).

During the period of discontinuation of clopidogrel, other short-acting and reversible antiplatelet or antithrombotic agents are administered. This is termed as bridging therapy. Some of such drugs include unfractionated heparin (UFH), subcutaneous injection of low-molecular-weight heparin, non-steroidal anti-inflammatory drugs, phosphodiesterase III inhibitor and GP IIb/IIIa inhibitors(DeVile & Foëx, 2010).

Cilostazol, a phosphodiesterase III inhibitor, shows antiplatelet effects due to inhibition of conversion of cyclic adenosine monophosphate (cAMP) to 5'-AMP within platelets(Lavie & DiNicolantonio, 2013; Lee et al., 2010). It possesses dual action of inhibiting both platelet activation and smooth muscle proliferation and possibly target two grievous complications of PCI, i.e., stent thrombosis and restenosis(Bangalore et al., 2014). It is transpiring as a promising drug for bridging therapy. Its action is reversible, it is administered orally and is short acting drug(Hall & Mazer, 2011); however, data regarding the effectiveness of cilostazol as bridging therapy are scarce. Thus, we intended to study the outcomes of use of aspirin and cilostazol as bridging therapy for periprocedural management of antiplatelet therapy in patients undergoing non-cardiac surgery within one year after drug eluting stents implantation.

Materials and methods

Study population and design

This was a single-centered, retrospective study conducted between September 2013 to March 2016. Nine patients who had undergone non-cardiac surgery with risk of bleeding were given aspirin and cilostazol with discontinuation of clopidogrel. Retrospective analysis by reviewing case sheets, operative notes and laboratory tests, was performed for documentation of the clinical details of patients' outcome. Inclusion criteria were patients with DES implantation within one year in whom non-cardiac surgery was to be performed and risk of periprocedural bleeding risk was high. All patients were discontinued clopidogrel prior to procedure. Aspirin was continued perioperatively and cilostazol was added as 50 mg two times a day from the day of discontinuation of clopidogrel and stopped 24 hours prior to procedure. Clopidogrel was restarted 24 hours after surgical procedure as 300 mg loading dose followed by maintenance dose of 75 mg daily.

Definitions

Major bleeding was defined as intracranial hemorrhage, gastrointestinal internal bleed, or bleed which requires two units of blood transfusion. Minor bleed is defined as no additional hospitalization or interventions needed to control bleed. Occurrence of stent thrombosis was determined as per the Academic Research Consortium definitions(Cutlip et al., 2007).

Results

Of nine patients, 6 were males and age of patients ranged between 48 and 73 yrs. The patients underwent non-cardiac surgery, one neurosurgery (subdural hematoma) and two urologic procedures, 2 gynecologic surgeries (Hysterectomy plus salpingo-oophorectomy), I radical mastectomy, 1 orthopedic surgery and two gastrointestinal malignancy surgeries. Clopidogrel discontinuation was done on an average of 4.4 days. The baseline and procedural characteristics of all patients have been detailed in **Table 1.**

There was no occurrence of stent thrombosis, nor were any death or acute coronary syndrome. Post operatively ECGs were taken 6 to 8 hours after procedure and blood samples were analyzed for troponin in 4 patients but none showed positivity. No major bleeding observed. Two patients had minor bleed (hematuria after TURP prostate surgery and one local bleed during orthopedic surgery (trochanteric fracture)), but none of them required blood transfusion.

Discussion

Patients necessitating non-cardiac surgery within 12 months of PCI, the major adverse cardiac event rates including cardiac death,

myocardial infarction, revascularization or bleeding of 4% to 45% have been documented. These rates depend on the time of surgery after stenting, continuation of antiplatelet therapy and type of stent implanted(Ka , Joseph, Lee, Raizner, & Raizner, 2000; M. Vicenzi et al., 2006; M. N. Vicenzi, Ribitsch, Luha, Klein, & Metzler, 2001; Wilson et al., 2003). The effect of these factors has been demonstrated in some studies. In a previous study that included 192 patients undergoing surgery within 2 years of PCI, reported a MACE rate of 13.3% in the early surgery group (duration of surgery after stenting was 1 month for bare-metal stents, 3 months for sirolimus-eluting stents, and 6 months for paclitaxel-eluting stents) and 0.6% in late surgery group (later than previous stated duration). Both antiplatelet agents were discontinued and there was no bridging therapy applied during intervention(Schouten et al., 2007). Similarly, in another study Vicenzi et al. observed 5 deaths, 12 myocardial infarctions, 8 re-PCIs and 5 cases of unstable angina pectoris out of total 103 patients who required non-cardiac surgery within 12 months of PCI. The risk of an event was 2.11 times higher in patients with surgery less than 35 days after stenting compared with patients with surgery more than 90 days after PCI(M. Vicenzi et al., 2006).

There are limited data concerning perioperative ST in patients with DES. In a meta-analysis, Burger et al.(Burger, CHEMNITIUS, Kneissl, & Rücker, 2005) included 49,590 patients who underwent noncardiac surgery and concluded that peri-procedural aspirin continuation led to an intensification in bleeding by a factor of 1.5. But, this rise did not lead to increase in severity of bleeding complications or fatal bleeding except in intracranial surgery and possibly transurethral prostatectomy. Besides, withdrawal of aspirin was linked with greater incidences of cardiac, cerebral, and peripheral vascular events(Abualsaud & Eisenberg, 2010). Thus, such situation necessitates the use of some antiplatelet drug along with aspirin.

On this background, it becomes apt to use fast-acting platelet inhibitor with relatively short duration of action for periprocedural management. Thus, we administered cilostazol and aspirin in 9 patients undergoing non-cardiac surgery within 12 months of PCI with DES. Clopidogrel was discontinued about an average of 4.4 days before surgery. Clopidogrel was restarted 24 hours after surgical procedure as 300 mg loading dose followed by maintenance dose of 75 mg daily. The bridging therapy in perioperative period was analogous to the consensus statement recommendations(Wessler, Saldana, & Giugliano, 2012). This study showed no stent thrombosis, ACS events or death within 30 days after surgical procedure. There were two incidences of minor bleeding, but without the need of blood transfusion. However, it is inappropriate to confirm efficacy with aspirin plus cilostazol as bridge to dual antiplatelet therapy due to small sample size.

Recently, the OUTSIDE START Cilostazol Bridging Study reported results of 95 patients with previous PES implantation, presently undergoing surgery, in whom DAPT was ceased and cilostazol was administered 100 mg BID from 7th pre-operation day. They concluded that cilostazol appeared reliable without major bleeding or MACE in high stent thrombosis risk PES patients and stated that similar success in current DES requires further confirmation in larger studies(Laham, Chandra, & Shammas, 2015).

Study Limitations

The sample size of our study is small and therefore it is not apt to conclude effectiveness of using cilostazol along with aspirin as bridging therapy. Also, there is no control group, thus incidence of adverse events without bridging in a similar population is unknown.

Conclusion

Perioperative management of patients with DES is a critical issue. Maintenance of dual antiplatelet therapy remains mainstay of the stent thrombosis prevention. In cases with high risk for bleeding, bridging therapy with aspirin plus cilostazol for periprocedural management of antiplatelet therapy is associated with low risk of stent thrombosis, however, larger studies would further confirm its efficacy.

Tables Table 1: Baseline and procedural characteristics of patients

Patient	Age(yr) / Sex	Number of Stents	Stent indication	Surgical Procedure	Duration from Angioplasty to surgical procedure (Months, days)	Days Clopidogrel held prior to surgery	Bleeding
1	56/ Female	1	Unstable angina	Abdominal hysterectomy and salpingo-oophorectomy	six months 7 days	4	None
2	65/ Male	2	NSTEMI	Colonic malignancy surgery	4 months 20 days	5	None
3	73/ Male	2	NSTEMI	TURP prostate surgery	6 months 28 days	5	Minor bleed
4	68/ Male	1	Unstable angina	Subdural hematoma evacuation	3 months 12 days	3	None
5	57/ Female	1	Acute AWMI	Radical mastectomy	8 months 5 days	5	None
6	63 / Male	2	Unstable angina	Bladder sessile polyp surgery	4 months 19 days	5	None
7	58/ Male	3	Stable angina	Total gastrectomy	8 months 12 days	4	None
8	48/ Male	2	NSTEMI	Trochanteric fracture	10 months 22 days	5	Minor bleed
9	56/ Female	1	Unstable angina	Cholecystectomy	3 months 3 days	4	None

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