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Coronary stent management in elective genitourinary surgery

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To review the literature on coronary stents and genitourinary surgery and provide a protocol for perioperative. The keywords, 'elective surgery', 'aspirin', 'clopidogrel', 'guidelines for percutaneous coronary intervention', and 'antiplatelet therapy after coronary stent placement' were used to search PubMed for any relevant articles relating to coronary stents. Recommendations were made based on the whether the procedures patients were exposed to placed them at low-, moderate- or high-bleeding risk based on the extent of the procedure. All elective procedures should be delayed for 1 month after bare-metal stent placement and 1 year after drug-eluting stent placement. In patients classified as low risk (endoscopy and laser prostatectomy), aspirin should be continued throughout the perioperative period and dual antiplatelet therapy should continue 24–48 h postoperatively, if there is no concern for active bleeding. In those classified as moderate risk (scrotal procedures, transurethral resection of bladder tumours, transurethral resection of the prostate, urinary sphincter placement) dual antiplatelet therapy should be discontinued 5–7 days before the procedure and continued within 7 days after procedure, if there is no concern for active bleeding, in consultation with cardiology. In high-risk procedures (cystectomy, nephrectomy, prostatectomy, penile prosthesis placement) dual antiplatelet therapy should be discontinued 10 days before the procedure and continued postoperatively within 7–10 days of the procedure, when there is no longer a concern for active bleeding with the assistance of a cardiologist. Coronary artery disease is becoming more prominent in our society, increasing the use of coronary stents and antiplatelet agents. With the proposed protocol, it is safe to proceed with surgical intervention in those that have adequate stent endothelialisation.

What's known on the subject? and What does the study add?
Withdrawal of dual antiplatelet therapy before the recommended, 12 months for drug-eluting stents and 1 month for bare-metal stents increases the rate of major adverse coronary events and mortality. However, in those undergoing surgery the risk of bleeding is increased substantially for those on antiplatelet agents. Successful management in patients with coronary stents who must undergo elective or non-elective urological surgery should be a multidisciplinary decision.

This article reviews the literature and recommends a protocol for clinical management of patients undergoing urological procedures after coronary stent placement.

KEYWORDS

antiplatelet, coronary stent, aspirin, clopidogrel, elective surgery

INTRODUCTION

About 1.8 million Americans will undergo a percutaneous coronary intervention (PCI) and receive one or more intracoronary stents, annually [1]. Current guidelines recommend 1 month of dual antiplatelet therapy for bare-metal coronary stents and 1 year of dual antiplatelet therapy for drug-eluting coronary stents [2]. The extensive use of dual antiplatelet therapy presents a significant dilemma for the perioperative management of this population undergoing genitourinary surgery.

Bare-metal stents (BMS) are thin expandable strut devices constructed from stainless steel alloys that scaffold open segments of atherosclerotic coronary arteries. In all, 25–30% of patients developed stent re-stenosis within the first year after BMS implantation requiring vessel revascularisation, either via repeat stenting or surgery [3]. In 2003, the USA Food and Drug Administration (FDA) approved the use of drug-eluting stents (DES), which are coated with a polymer that releases anti-proliferative and anti-inflammatory drugs that have been shown to decrease stent re-stenosis by nearly 70%. Although DES markedly decrease intimal hyperplasia, they also simultaneously increase the time required for stent endothelialisation [3,4] and therefore require a much longer period of dual anti-platelet therapy to reduce the risk of stent thrombosis.

METHODS

The following keywords were used to search PubMed for any article relating to coronary stents: 'elective surgery', 'aspirin', 'clopidogrel', 'guidelines for percutaneous coronary intervention', and 'antiplatelet therapy after coronary stent placement'. The articles were then reviewed. The American Heart Association (AHA) guidelines for management of patients after PCI were also included.

COMPLICATIONS

Discontinuing oral antiplatelet therapy prematurely has been shown to increase

rates of re-admission and mortality in patients after undergoing DES placement [5]. Withdrawal of aspirin therapy is an independent predictor of mortality in patients who have coronary artery disease. There was a three-fold higher rate of mortality in patients with coronary artery disease who discontinued aspirin therapy against recommendations, but there was a significantly higher risk of mortality in those who had previously had coronary stent placement [6].

Abrupt discontinuation of antiplatelet therapy results in a dramatic rebound in the inflammatory and prothrombotic state, which promotes platelet aggregation. These changes are further compounded by the perioperative state that is accompanied by increases in cytokines and other inflammatory mediators that activate platelets and the coagulation cascade and impairs fibrinolysis. The addition of this physiological state in the setting of an incompletely endothelialised stent significantly increases the probability of stent thrombosis.

Stent thrombosis is the result of platelet activation and the most prominent risk factor is the discontinuation of dual antiplatelet therapy before stent endothelialisation. Once stent endothelialisation occurs the risk of stent thrombosis is reduced significantly if antiplatelet therapy is withdrawn. However, no clinical test to determine the level of endothelialisation exists to determine the safety of discontinuing dual antiplatelet therapy in these patients [3].

ANTIPLATELET THERAPY

Thromboxane A2 is synthesized and released by activated platelets and plays a crucial role in the activation of surrounding platelets promoting their incorporation into the haemostatic platelet plug. The anti-platelet effects of aspirin are mediated by its ability to irreversibly bind to the enzyme cyclooxygenase 1 (COX1) and inhibit its synthesis of thromboxane A2. As aspirin irreversibly binds to COX1 and platelets are anucleate cells, aspirin-mediated platelet inhibition lasts for the duration of the platelet's lifespan (7–10 days). In contrast, other NSAIDs, e.g. ibuprofen and naproxen, are reversible COX1 inhibitors such that their antiplatelet effects only last as long as significant concentrations of drug remain in the blood stream (i.e. half-lives, 12 h for ibuprofen, 65 h for naproxen and up to 5 days for meloxicam).

Thienopryidines (clopidigrel, ticlopidine, prasugrel) bind irreversibly to the ADP $P2Y_{12}$ receptor inhibiting activation of the ADP-mediated glycoprotein GPIIb/IIIa complex, which is essential in mediating the final common pathway of platelet aggregation. Therefore, these medications should also be discontinued 7–10 days preoperatively to ensure the return of normal platelet function before surgery.

ELECTIVE SURGERY

About 5% of patients within the first year after intracoronary stent placement will undergo non-cardiac surgery [7]. Two large retrospective studies examined the incidence of major adverse cardiac events (MACE) in the perioperative period of non-cardiac surgery in patients with BMS and DES in relationship to the time from intracoronary stent placement. Patients with BMS had a significantly lower risk of MACE when non-cardiac surgery took place ≥30 days after stent placement (10.4% vs 3.8%) [7]. Patients with DES had a lower incidence of MACE when undergoing non-cardiac surgery ≥1 year after PCI (6.0% vs 3.3%); however, this difference was not as significant as for BMS recipients at 1 year [8]. These studies have helped form the basis for the FDA recommendations and American College of Cardiology/AHA guidelines for dual antiplatelet therapy in patients with intracoronary stents [2].

PERIOPERATIVE MANAGEMENT

The most important decision regarding the perioperative management of patients with intracoronary stents is to carefully weigh the risks of bleeding associated with continued anti-platelet therapy compared with the risks of stent thrombosis upon discontinuation. Elective surgical procedures should be postponed until after the initial requirement for dual antiplatelet therapy is completed, allowing for proper stent endothelialisation (a minimum of 1 month for BMS and 12 months for DES) [2]. Management of more complicated (complex or multiple high-risk stents) patients in the perioperative phase should be multidisciplinary including a cardiologist, haematologist, anaesthesiologist and the surgeon.

There are limited data available for evidence-based decision making for perioperative anti-platelet agent management in urology patients. Retrospective studies of patients undergoing traditional approaches to TURP found an increased risk of postoperative bleeding associated with perioperative aspirin use [9,10]. However, more recent retrospective observational studies using photoselective laser vaporization of the prostate found no significant difference in blood loss between patients taking clopidogrel or aspirin or warfarin compared with control patients [11,12]. In a randomised double-blind placebo-controlled trial, Nielsen *et al.* [13] reported increased blood loss but no increase in transfusion requirements in patients taking 350 mg aspirin daily before TURP compared with placebo recipients. A retrospective cohort study by Wierod *et al.* [14] reported increased blood product use among TURP patients taking aspirin or NSAIDs.

Aspirin therapy (350 mg daily) and clopidogrel both have been associated with haematoma formation in patients undergoing external shockwave lithotripsy [15,16]. In contrast, a prospective patient questionnaire found no increase in haematuria or overall bleeding in patients taking aspirin undergoing transrectal prostate biopsy [17]. However, a second larger study reported patients taking aspirin had a higher incidence of haematuria and rectal bleeding [18]. A prospective randomised trial of 200 patients undergoing transrectal prostate biopsy found that low dose aspirin (100 mg daily) increased the duration of haematuria and rectal bleeding [18]. No data exist for patients undergoing major urological surgery, e.g. nephrectomy, cystoprostatectomy or prostatectomy. However, a retrospective review of >1000 patients that underwent partial nephrectomy noted no increase in bleeding among patients taking warfarin, aspirin or clopidogrel when these medications were discontinued at, 5 days for warfarin, 10 days for clopidogrel, and 7–10 days for aspirin, before surgery [19]. Similar results were published for patients undergoing nephrolithotomy [20]. A survey of British Urologists reported that 62% ask patients to

TABLE 1 Recommendations for perioperative antiplatelet management after initial dual antiplatelet therapy (1 month for BMS and 1 year for DES) is completed

Bleeding risk category	Type of procedure	Preoperative modifications	Resuming antiplatelet therapy
Low	Endoscopy (cystoscopy, ureteroscopy), laser lithotripsy, laser prostatectomy, urethral bulking procedures	Continue aspirin through perioperative period. Discontinue clopidogrel.	Re-start clopidogrel within 24–48 h postoperatively, if no concern for postoperative bleeding
Moderate	TRUS, TURBT, ESWL, TURP, scrotal procedures, urinary sphincter placement, sling placements, female prolapse repair	Discontinue aspirin and clopidogrel therapy 5–7 days before procedure	Re-start dual antiplatelet therapy within 7 days of procedure, if no concern for postoperative bleeding in coordination with cardiologist
High	Nephrectomy, cystectomy, prostatectomy, partial nephrectomy, penectomy, penile prosthesis placement	Discontinue dual antiplatelet therapy 10 days before procedure	Re-start antiplatelet therapy when no concern for active bleeding in coordination with cardiologist (7–10 days after no active bleeding)

TURBT, transurethral resection of bladder tumours; ESWL, extracorporeal shock wave lithotripsy.

stop aspirin a median of 10 days before TURP [21]. More than 90% of urologists stop clopidogrel before urological surgery and 43% do not routinely prescribe bridging anti-platelet therapy for their patients [22].

Most studies exploring the effect of aspirin in the perioperative period involve cardiac and vascular procedures where the outcome of the grafts are improved and the effect on bleeding is increased by 1.5 but with no significant impact on mortality or morbidity. The studies evaluating the effect of clopidogrel administration during the perioperative period primarily have been done in cardiac surgeries and the data are conflicting. Patients on dual aspirin and clopidogrel therapy do have a 3.4-fold longer bleeding time. The indication of dual antiplatelet therapy in patients with coronary stent placement is always accompanied with the administration of aspirin. The combination of clopidogrel and aspirin increases the absolute risk of bleeding by 1.0% when compared with those undergoing non-cardiac surgery on aspirin alone [1]. At least one randomised controlled trial indicates that re-institution of aspirin once haemostasis is achieved postoperatively is associated with no increase in bleeding complications [23].

RECOMMENDATIONS [TABLE 1]

The above recommendations are based on the review of the literature and the current AHA guidelines. Procedures where the risk of bleeding is relatively low and the initial duration of dual antiplatelet therapy is completed, such as endourological procedures that are anticipated to be short, it is reasonable to continue aspirin therapy throughout the perioperative period, especially if the patient is at increased risk of a thrombotic event. The continuation of dual antiplatelet therapy in a low-risk setting is still not favourable given the small but real risk of complications requiring an ultimately more invasive procedure.

Procedures that have a moderate bleeding risk if performed with concurrent aspirin therapy vs complete withdrawal of antiplatelet therapy, necessitate a decision that should be made with the help of the operating surgeon and the patient's cardiologist. If another non-invasive treatment method is available then it should be considered as an alternative to surgery. If such an option is not available then the risk of major bleeding in the perioperative phase vs the risk of coronary compromise with a thrombosis should be compared and discussed with the patient.

When surgical procedures associated with a high risk of bleeding are necessary, then complete withdrawal of antiplatelet therapy is required or another non-invasive therapy should be chosen. A multidisciplinary approach, including a cardiologist, surgeon and anaesthesiologist, to the perioperative management of these patients is crucial in all procedures, because the patient's individual risk factors, history and the surgeon's familiarity with the procedure are all factors that will play a role in clinical decision making.

Prasugrel, an irreversible ADP receptor blocker, similar to clopidogrel has a faster onset of action, less individual variability of action and is a more powerful platelet inhibitor. It is also associated with a higher rate of clinical bleeding. Ticagrelor, an oral reversible antiplatelet $P2Y_{12}$ receptor inhibitor, recently approved by the FDA, has been shown to have increased efficacy compared with clopidogrel without an increased rate of bleeding [24]. The use of prasugrel and ticagrelor have not been addressed in treatment guidelines, therefore the guidelines for clopidogrel have been applied.

In a life-threatening situation when the procedure cannot be delayed, the idea of bridging therapy with unfractionated heparin, low-molecular-weight heparin, direct thrombin inhibitors or glycoprotein IIb/IIIa inhibitors have been proposed in the literature [25,26]. However, there is no evidence to suggest that bridging with these agents does in fact improve survival. The American College of Chest Physicians recommends to continue on with the procedure through dual antiplatelet therapy given the elevated risk of stent thrombosis while understanding the increased risk of severe bleeding without the use of bridging therapy [25,26].

There has been an experimental protocol, effective in a single centre, developed for patients with recent DES placement in whom surgery should not be delayed. The bridging therapy with tirofaban, a short acting GPIIb/IIIa receptor blocker, is recommended to start 3 days before surgery and clopidogrel is discontinued 5 days before surgery. Tirofaban is stopped 4 h before the procedure and resumed 4 h after, if oral administration of drugs is not possible. The recommendations outline for clopidogrel to start as soon as oral administration is possible. Low-dose aspirin is continued throughout the perioperative course along with deep venous thrombosis prophylaxis. This protocol should only be practiced in a facility with a coronary care unit, for postoperative admission, and equipped for urgent revascularisation if necessary [27]. This may benefit the perioperative outcomes for the patient population that needs surgery during the period of incomplete stent endothelialisation.

CONCLUSION

As the sheer number of patients with coronary stents and on antiplatelet therapy continues to grow, evidence-based protocol for patients on antiplatelet therapy becomes necessary. For optimal outcomes it is clear that a multidisciplinary approach, including a cardiologist, surgeon, and anaesthesiologist, is ideal for a careful assessment of thrombotic and bleeding risks. Table 1 allows for management strategies for most patients, undergoing urological intervention; however, more data is needed to develop evidence-based guidelines for more thorough perioperative management.

CONFLICT OF INTEREST

None declared.

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Abbreviations: **PCI**, percutaneous coronary intervention; **BMS**, bare-metal stents; **FDA**, USA Food and Drug Administration; **DES**, drug-eluting stents; **AHA**, American Heart Association; **COX1**, cyclooxygenase 1; **MACE**, major adverse cardiac events.