Review Article

Perioperative dual antiplatelet therapy for patients undergoing spine surgery soon after drug eluting stent placement

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INTRODUCTION

At least 6–12 months of dual antiplatelet therapy (DAPT) are routinely utilized after placement of drug-eluting coronary stents (DES).[⁷] For patients requiring urgent or emergent spinal surgery within 6 months of undergoing a PCI for DES placement is challenging. As early interruption of DAPT may have catastrophic consequences, we hereby proposed a novel protocol involving stopping clopidogrel 5 days before and aspirin 3 days before spine surgery, and bridging the interval with a reversible P2Y12 inhibitor until surgery. Moreover, postoperatively, aspirin could be started on postoperative day 1 and clopidogrel on day 2. Nevertheless, this treatment strategy may not be appropriate for all patients, and multidisciplinary approval of perioperative antiplatelet therapy management protocols is essential.

Keywords: Cangrelor, Drug-eluting stent, Dual antiplatelet therapy, Emergent spine surgery, P2Y12 inhibitor
6 months of cardiac stent placement, the risks of continuing (i.e. perioperative spinal hemorrhage resulting in severe disability or even death) versus stopping (i.e., acute stent thrombosis or even death) DAPT must be carefully weighed.\textsuperscript{[9]}

Here, we reviewed the literature regarding the feasibility and safety of performing urgent spinal surgery for patients on DAPT soon after DES placement utilizing a novel approach. The latter involves cessation of clopidogrel (5 days) and aspirin (3 days) preoperatively with postoperative reinstitution of aspirin (postoperative day 1) and clopidogrel (postoperative day 2).

MATERIALS AND METHODS

Important variables when considering surgery in a patient on DAPT for recent cardiac stent placement: (1) the urgency of the surgery, (2) the type of percutaneous cardiac intervention (PCI) (balloon angioplasty vs. stenting), (3) the stent type (drug-eluting vs. balloon mechanical stent), and (4) the PCI to noncardiac surgery time interval.\textsuperscript{[10]}

A thorough PubMed search yielded 510 papers on the topic. Critical variables studied included: outcomes of post-PCI patients undergoing emergent spine surgery while on DAPT, perioperative anticoagulation guidelines, and alternative drugs that lessen the risk of bleeding without increasing the risk of stent thrombosis.

RESULTS

Guidelines for DAPT and timing of noncardiac surgery after PCI [Table 1]

The American College of Cardiology, American Heart Association, and European Society of Cardiology have relatively congruent guidelines regarding the necessity of DAPT for patients with acute coronary syndrome who have undergone PCI with the placement of DES.\textsuperscript{[4,7,9,10]}

However, the duration of treatment remains controversial. Most current guidelines require 6–12 months of DAPT with aspirin and clopidogrel after PCI revascularization, with continuation of aspirin recommended indefinitely [Table 1].

The guidelines currently recommend waiting at least 1 year before any noncardiac surgery after DES placement, to allow sufficient time for endothelialization.\textsuperscript{[9]} Notably, the highest risk for stent thrombosis is within the first 6 weeks after stent placement.\textsuperscript{[9]}

Urgent surgical treatment for cervical spondylotic myelopathy (CSM): indications and management

With rapidly progressing CSM, postponing surgery risks permanent severe disability. Treatment options for CSM include corpectomy and fusion, anterior cervical discectomy and fusion, posterior cervical decompression (with or without fusion), or any combination thereof.\textsuperscript{[9,13]}

Alternatively, if the patient is only minimally symptomatic, delaying surgery is a more reasonable option.\textsuperscript{[6]}

| Reference(s)          | Findings                                                                                           |
|-----------------------|----------------------------------------------------------------------------------------------------|
| Dimitrova et al., 2012\textsuperscript{[4]} | Current DAPT guidelines and practice: 6–12 mos DAPT with aspirin and clopidogrel after PCI, aspirin indefinitely |
| Roth et al., 2012\textsuperscript{[9]}    | RCTs demonstrate no significant difference in MACEs between short (3–6 mos) and long-term (12 mos) DAPT |
| Singla et al., 2012\textsuperscript{[10]}  | Study demonstrating no appreciable difference in MACEs between 6–12 mos and > 12 mos DAPT            |
| Levine et al., 2016\textsuperscript{[7]}   | Highest complication rate during first 6 weeks after stent placement (mainly stent thrombosis)     |
| Vankuijk et al. Timing of noncardiac surgery after coronary artery stenting with bare metal or drug-eluting stents. Am J Cardiol 2009; 104:1229-3 | Higher risk of stent thrombosis with EF<50%, renal insufficiency, diabetes, malignancy, or bifurcated stented vessel |
| Roth et al., 2012\textsuperscript{[9]}    | Interindividual variance for many antiplatelet agents (i.e., clopidogrel)                           |
| Roth et al., 2012\textsuperscript{[9]}    | Sudden cessation of DAPT can cause a reflex prothrombotic state contributing to stent thrombosis secondary to upregulation of platelet biomarkers and a pro-inflammatory response |
| Gurbel PA, DiChiara J, Tantry US. Antiplatelet Therapy After Implantation of Drug-Eluting Stents: Duration, Resistance, Alternatives, and Management of Surgical Patients. American Journal of Cardiology 2007; 100:S18-25 | Wait at least 1 year before any noncardiac surgery after DES placement |
| Singla et al., 2012\textsuperscript{[10]}  | DAPT: Dual antiplatelet therapy, DES: Drug-eluting stent, EF: Ejection fraction, MACEs: Major adverse cardiac events, PCI: Percutaneous cardiac intervention, RCT: Randomized control trial |

Perioperative management of DAPT for major noncardiac surgery soon after PCI [Table 2]

The Clopidogrel in Unstable Angina to Prevent Recurrent Events study and others concluded that patients on both aspirin and clopidogrel are more likely to have major bleeding events and bleeding complications with surgical interventions (3.4-fold) than those solely on aspirin (1.5-fold) [Table 2].\textsuperscript{[5,9]}

This bleeding risk is particularly concerning
for spinal operations where any hemorrhage may result in catastrophic disability.

However, as the sudden cessation of DAPT can cause a reflex prothrombotic state possibly contributing to stent thrombosis, an antiplatelet “bridge” is recommended perioperatively.\cite{9}

**Bridging protocol recommendations** [Table 3]

No standard of care exists regarding perioperative management of patients with DES on DAPT undergoing spine surgery. Some recommend holding DAPT up to five half-lives before surgery and starting a bridging agent within 12 months of the PCI to minimize ischemic cardiac events.\cite{9}

When selecting a bridging agent, critical characteristics to consider include reversibility and a short half-life.\cite{9}

Bridging agents include GP IIb/IIIa receptor inhibitors which interfere with fibrinogen, oral irreversible P2Y12 receptor inhibitors, and thrombin protease-activated receptor inhibitors. Postoperatively, both aspirin and clopidogrel can be safely restarted on postoperative day 1 or 2 with loading doses [Table 3].\cite{2}

Interestingly, one study showed that bridging with low-molecular-weight heparin was linked to more major adverse cardiac and cerebrovascular events and bleeding complications versus remaining on DAPT perioperatively.\cite{3}

**Promise of cangrelor**

Cangrelor, a reversible, intravenous P2Y12 inhibitor with rapid onset and return to baseline platelet function when discontinued may be considered as a new bridging agent [Figure 1].\cite{1,11}

Its safety and efficacy as a bridging agent have been established in the BRIDGE trial for patients undergoing coronary artery bypass grafting.\cite{11}

They found no excessive bleeding or significant increase in ischemic events.\cite{11}

The Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition trials demonstrated reduced stent thrombosis in the cangrelor group and comparable bleeding rates relative to the clopidogrel group.\cite{1}

Nonetheless, a drug application for the use of cangrelor in post-PCI patients as a bridging therapy in noncardiac surgeries was initially denied by the FDA in 2014; however, the drug was recently approved in 2016 for pretreatment in PCI patients only.\cite{12}

**Table 2:** Summary of current evidence-based data regarding perioperative DAPT in major noncardiac surgery soon after PCI.

| Reference(s)                                                                 | Findings                                                                 |
|------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Singla et al., 2012\cite{10}                                                  | Continuing aspirin during spinal surgery did not show a significant increase in bleeding, operation time, or postoperative blood transfusion compared to no perioperative antiplatelet therapy. |
| Akhavan-Sigari R, Rohde V, Abili M. Continuation of medically necessary platelet aggregation inhibitors - acetylsalicylic acid and clopidogrel - during surgery for spinal degenerative disorders: Results in 100 patients. Surg Neurol Int 2014; 5:S376-9 | No increased risk of bleeding in patients undergoing elective spinal surgery and receiving aspirin and clopidogrel compared to aspirin alone before surgery. |
| Gerschutz and Bhatt, 2002\cite{9}                                            | Patients on aspirin and clopidogrel are more likely to have major bleeding events with surgical interventions than those on aspirin alone. |

**Figure 1:** Illustration of the mechanism of action of the various groups of antiplatelet agents.
CONCLUSION

There is a great concern regarding the lack of clear guidelines for perioperative antiplatelet therapy for patients requiring urgent or emergent spine surgery within 6 months of PCI with DES implantation. We propose a novel protocol in which clopidogrel and aspirin are stopped 5 and 3 days before surgery, respectively, a reversible P2Y12 inhibitor such as cangrelor is used as bridging agent until the time of surgery, and postoperatively, aspirin and clopidogrel may be restarted on postoperative day 1 and 2, respectively.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors. For this type of study, formal consent is not required.

Declaration of patient consent

Patient’s consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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