



Thoracoscopic surgery for lung cancer without interruption of anti-platelet agents: is it really safe?

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Recently, thoracoscopic surgery has expanded globally as a minimally invasive alternative for thoracotomy because of its low invasiveness and painless aspect and the extremely good self-reported quality of life following this surgery (1). Elderly patients with several complications who have been diagnosed with lung cancer are highly appropriate candidates for thoracoscopic resection (2). In this regard, a number of operative cases present with several underlying diseases, ischemic heart disease, cerebral infarction and several autoimmune diseases. When those patients undergo an operation, they should be checked for prescribed drugs, and anti-platelet agents (APAs) should be discontinued in order to prevent complications such as bleeding associated with anesthetic and perioperative treatments. Simultaneously, surgeons must also be alert for thrombus due to the interruption of these APAs during the perioperative period.

A collaborative meta-analysis of randomized trials of antiplatelet therapy for preventing occlusive vascular events in high-risk patients (3) found that the allocation to antiplatelet therapy reduced the combined outcomes of any serious vascular events by about one-quarter; non-fatal myocardial infarction was reduced by one-third and non-fatal stroke by one-quarter. The study concluded that aspirin is protective in most types of patient at increased risk of occlusive vascular events, including those with ischemic heart disease or cerebral ischemia, or atrial fibrillation. Faced with the decision to either discontinue or continue APAs in patients undergoing non-cardiac operations, the cardiovascular risks associated with the perioperative withdrawal of APAs and the bleeding risks

associated with their continuation should be weighed and considered. Secondary prevention with low-dose aspirin reduces the risk of stroke and myocardial infarction and more significantly the risk of cardiovascular death (3). Most guidelines therefore propose the continuation of antiplatelet monotherapy (with either aspirin or clopidogrel) for non-cardiac operations, as the benefits outweigh the bleeding risk (4,5).

Several studies regarding the perioperative continuation of anti-platelet therapy have reported that the surgeries were performed safely in patients continuing APAs (mainly aspirin), and that the risk of bleeding and associated complications was almost the same as in the non-prescribed patients (6-9). In addition, those studies proposed several exceptions to the recommendation, including intracranial procedures, transurethral prostatectomy and operations with an extremely high bleeding risk. Only two randomized controlled trials (RCT) have assessed the primary outcome of bleeding and thrombotic risk when continuing APAs. Mantz *et al.* (10) reported the results of a RCT in 291 patients (145 aspirin-treated cases and 146 placebo cases), which included cases of orthopedic surgery (52.2%), abdominal surgery (20.6%) and urologic surgery (15.5%). No significant difference was found in the number of major complications between the two treatment groups. Another RCT examined the effects of continuation or discontinuation of aspirin before surgery. In this trial by Oscarsson *et al.* (11), myocardial damage, defined as the elevation of troponin T, was chosen as the primary endpoint. Four patients (3.7%) in the group receiving aspirin and ten patients (9%) in the group receiving a placebo experienced

myocardial damage. While this difference did not reach statistical significance, nine patients in the placebo group suffered major postoperative cardiac events (cardiovascular death, myocardial infarction and severe arrhythmia during the first 30 postoperative days) in contrast to three patients in the aspirin group ($P=0.02$). However, conflicting results have also been reported; in a large-scale RCT investigating the safety and benefits of aspirin prescription before non-cardiac surgery and throughout the early postsurgical period, Devereaux *et al.* reported no significant effects on the rates of either death or nonfatal myocardial infarction, and the risk of major bleeding events was elevated in the aspirin-prescribed patients (12). In contrast to previous RCTs or reviews, Devereaux *et al.* did not set any limit on the candidates of patients with respect to their history of vascular disease. On limiting our investigation of previous perioperative APA studies to those involving general thoracic surgery, we uncovered a few reported studies. Yu *et al.* (13) reported on the safety of thoracoscopic surgery for patients with lung cancer receiving APAs in their retrospective study of 164 patients (106 patients who stopped APA administration and 58 who continued it). They concluded that continuing APAs did not markedly influence the perioperative risk of bleeding, but reduced the risk of cardiac and thrombotic events.

Cerfolio *et al.* (14) conducted a prospective study using a propensity score in 33 patients receiving clopidogrel at the time of surgery and 132 controls. The most common procedures were thoracotomy with lobectomy in 11 patients, video-assisted wedge resection in 6, mediastinoscopy in 4 and Ivor Lewis esophagogastrrectomy in 2. They observed no intraoperative morbidities nor bleeding events in the cases of primary thoracotomy, but two of the four patients who underwent redo thoracotomy had bleeding that required transfusions. None of the 8 patients receiving clopidogrel who had a coronary artery stent and underwent lobectomy had a perioperative myocardial infarction, whereas 5 of the 14 control patients undergoing lobectomy who had a coronary artery stent did ($P=0.05$). Thoracic surgery mainly for lung cancer carries an intermediate risk of bleeding when performed in the early stage of the disease. However, in cases of pleural adhesion, including redo operations, the procedure can occasionally carry a high risk of bleeding. It is difficult to predict the grade of pleural adhesion before surgery by computed tomography (CT). Thus, the crucial decision of whether or not to continue APA administration should be made by discussing the general health condition of each patient

with the treating cardiologist and anesthesiologist. The intraoperative control of bleeding for patients taking APAs seems to be more difficult than for patients not on these medications. However, most studies have found that the rate of reoperation was not markedly high among patients taking APAs who undergo non-cardiac operations (15).

Concerning the problem of bleeding caused by perioperative antiplatelet therapy, a moderately high risk of reoperation has been reported among patients receiving dual antiplatelet therapy (16). A similar result was reported by Yu *et al.* (13). Aspirin is the most widely studied and most commonly used APA. With regard to other antiplatelet drugs, clopidogrel has been shown to reduce serious vascular events by 10% compared with aspirin (17), but large-scale randomized evidence of the effects of clopidogrel versus aspirin is only available from a few studies. While aspirin, which is frequently used to prevent secondary cardiac events, is the most widely studied APA, few studies have extensively examined clopidogrel. Regarding the withdrawal of aspirin, several studies conducted in patients at intermediate and high risk of adverse events around surgery have shown a positive result in preventing perioperative cardiovascular complications by continuing APAs for patients with basic cardiovascular diseases (8,9). As such, when deciding on the perioperative withdrawal of APAs, the surgical risks, such as the invasiveness of the procedure, the cardiovascular condition of the patient and the cerebrospinal therapeutic situation, should be taken into careful consideration.

Concerning the combined treatment with both aspirin and clopidogrel, the rates of bleeding complications and transfusion cases are increased with such a regimen. Yu *et al.* (13) recommend the use of aspirin as a prescribed APA, while Cerfolio *et al.* (14) recommend the use of clopidogrel. These authors warn of continuing combination treatment with aspirin and clopidogrel in the perioperative period and urge limits on the use of aspirin or clopidogrel due to the high risk of cardiovascular events on the withdrawal of either. An analysis limited to the patients administered both aspirin and clopidogrel revealed an increased risk of postoperative bleeding and transfusion requirements, so it may be best to continue aspirin only in such patients.

Most preceding studies were not based on RCTs. Perioperative APA treatment does not increase the incidence of bleeding events following major operations, including thoracoscopic surgery. The current literature reviews support the continuation of aspirin for secondary prevention in patients at risk of cardiovascular events

who are undergoing most surgeries. The withdrawal of perioperative aspirin increases the risk of perioperative cardiovascular events but does not affect the level of severity of bleeding complications or the perioperative mortality due to bleeding complications (7-9). In conclusion, the decision to continue or discontinue APAs should be based on the severity of the cardiovascular or cerebrovascular comorbidities and should be made following consultation with the treating cardiologist and anesthesiologist on each operative case.

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