



Management of On-going Antiplatelet Treatment in Elderly Patients with Hip Fracture

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Editorial

About 10% of patients referred for hip fracture are in P2Y12 receptor antagonists treatment (clopidogrel, prasugrel or ticagrelor) at the moment of trauma. Inhibitors of P2Y12 receptor are administered with aspirin as “dual antiplatelet therapy” after percutaneous coronary revascularization, in particular prasugrel and ticagrelor have only this indication. In a not negligible number of subjects however clopidogrel is used in primary or secondary prevention of cardiovascular events in alternative to aspirin. P2Y12 inhibition causes prolonged platelet inactivation. Full recovery of platelet function is expected only 7 days after the last dose of these drugs. Therefore patients treated with P2Y12 receptor antagonists who need urgent/emergency non cardiac surgery have an increased risk of bleeding. In patients needing surgery within a few days, current ESC Guidelines recommend withholding clopidogrel and ticagrelor for five days and prasugrel for seven days prior to surgery [1]. Nevertheless the risk should be weighed against the risk of thrombosis in particular in patients underwent recent revascularization with medicated stents. For last generation medicated stents temporary suspension of dual antiplatelet agents may be considered 1 to 3 months after procedure.

Patients with hip fracture represent a relevant problem both from an epidemiological and clinical point of view. Early surgery (within 24-48 hours) is associated with a better outcome, both in terms of early (30 days) and long term mortality other than with improved functional recovery [2-3]. The British Orthopaedic Association recommends operation within 48 hours of admission for medically fit patients [4]. The risks associated with the operative management of patients on double antiplatelet agents include increased intra-operative bleeding and a higher risk of spinal haematoma where regional anaesthesia is used. Usually anesthesiologists and surgeons retain restoration of coagulative activity as a primary need. However, since results of hip fracture treatment are closely time-dependent, the mean time to surgery of 8 days reported after withdrawal of antiplatelet agents is unacceptable [5], being delayed surgery associated with higher complication rate and mortality.

In the attempt to give a clinical guide in the last five years several papers examined the effects of P2Y12 inhibitors continuation in patients undergoing hip fracture surgery. These investigations however suffer from several limits: first no randomized studies have been published, second most studies involve a small number of patients therefore meta-analysis were needed, third no information about the indication for treatment are reported (is clearly different the risk in patients with recent revascularization in comparison to patients in primary or secondary prevention), fourth patients in antiplatelet agents have on average complex medical co-morbidities and an higher ASA risk, finally no information exist on prasugrel or ticagrelor.

From available data two main questions should be answered: First is early hip fracture surgery for patients on clopidogrel (or prasugrel / ticagrelor) associated with worse postoperative outcomes compared

to patients not in P2Y12 inhibitors treatment? Second is early versus delayed surgery for these patients associated with worse postoperative outcomes?

Leonidou et al. [5] reported an average time to surgery of 8 days in 27 patients in clopidogrel at admission in comparison to 2.3 days in 378 control patients. Medical complications were more frequent and in hospital mortality higher in patients on clopidogrel at admission, although the difference was not statistically significant.

Feely [6] in a retrospective study identified 120 patients who were or not taking clopidogrel at the time of hip fracture. Mean time to surgery was less than 36 hours from admission in both groups. Perioperative bleeding complications and mortality were not significantly different between patients who were and were not taking clopidogrel at the time of hip fracture surgery. One-year mortality was 28% in the clopidogrel cohort and 29% in the control cohort (hazard ratio, 1.33; 95% CI, 0.84-2.12; P=0.23).

In a cohort study conducted in China 32 patients in clopidogrel were compared to 206 patients as control group [7]. Patients in clopidogrel treatment had a higher American Society of Anesthesiologists (ASA) grade and higher number of previous coronary stenting (P=0.002 and P<0.001, respectively). The rate of intraoperative blood transfusion, length of ICU stay, and overall hospital stay were higher in the clopidogrel group (all P<0.001). Postoperative complications were similar in the 2 groups. The 1-year mortality rate after surgery was significantly higher in the clopidogrel group compared with the control group (37.5% vs. 20.3%, P=0.030). Patients in clopidogrel treatment had a poorer prognosis after treatment of hip fracture in comparison to controls, however they had at admission an average higher ASA grade and more frequent previous arterial stenting therefore being a population at higher preoperative risk.

In a retrospective study were included 39 patients with hip fracture treated with clopidogrel [8]. Total blood loss, amount of blood transfusion and rate of postoperative complications were compared between the period 2011 to 2013 in which patients underwent delayed surgery, five days or more after clopidogrel withdrawal, and the period from 2014 to 2016 in which patients underwent early surgery, within 48 hours of admission. Although none of the end points differ between the two groups the author reported a different timing of bleeding. In the delayed surgery group it was noticed before surgery while it occurred

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Received: February 08, 2018; Accepted: February 10, 2018; Published: February 15, 2018

Citation: Rostagno C (2018) Management of On-going Antiplatelet Treatment in Elderly Patients with Hip Fracture. J Perioper Med 1: e101.

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during the intra-operative phase in the early surgery group. Early surgery group had a significant lower length of hospital stay: 11 ± 3 vs. 15 ± 4 days ($p=0.004$).

A systematic review identified after exclusion criteria 14 out of 4321 studies about the effects of clopidogrel in surgery for hip fracture [9]. All 14 were case series with controls. Odds ratio for transfusion was 1.24 (95% confidence interval 0.91 to 1.71), not statistically significant ($p=0.14$). The authors conclude that clopidogrel, if possible, should not be withheld throughout the perioperative period due to increased risk of cardiovascular events associated with stopping clopidogrel. Doleman et al. [10] compared results from patients undergoing early surgery on clopidogrel to a control group not taking clopidogrel. In patients in clopidogrel undergoing early surgery in hospital and 30-day mortality were not significantly increased (OR 1.10 95% CI: 0.48-2.54) although the need for blood transfusion significantly higher than in control group (OR 1.41 95% CI: 1.00-1.99).

Similarly in the meta analysis by Mattesi et al. [11], which included nine articles, early surgical management (<48 h) of patients receiving clopidogrel was demonstrated not to increase mortality at 30 days, 3 months or 1 year (between 25 and 30% mortality at 1 year). Perioperative bleeding was not significantly increased in patients receiving clopidogrel. Morbidity and mortality are not increased in these patients if surgery is performed immediately or less than 48 h after admission.

On the basis of previously reported data and of our own experience on more than one hundred patients we will try to answer to the 2 questions:

Is early hip fracture surgery for patients on clopidogrel (or prasugrel/tigacrelor) associated with worse postoperative outcomes compared to patients not in P2Y12 inhibitors treatment? In hospital outcome in patients who need hip fracture surgery treated with clopidogrel (and in our experience, although limited to a dozen of patients, also in dual antiplatelet treatment with aspirin and prasugrel or tigacrelor) is not significantly different from controls. In particular none of the studies reported an increase in mortality and length of hospitalization. The risk of bleeding on average was higher in patients treated with P2Y12 inhibitors with sometimes the need for 1 more blood unit transfusion. It is not surprising that long term mortality is higher in patients in antiplatelet treatment since they more frequently suffer from severe cardiovascular diseases before trauma. Second is early versus delayed surgery for these patients associated with worse postoperative outcomes? Although the data are limited a delay in hip fracture surgery is associated with a worse postoperative outcome, to a higher rate of complications and finally to a longer hospital stay.

In conclusion, in agreement with other authors, we believe that surgical delay in treatment of hip fracture is not justified in patients

in treatment with clopidogrel and the intervention may be performed general anesthesia (except if contraindicated) in the first 48 hours after trauma [12-14]. In patients in whom surgery must be postponed since they require medical stabilization the withdrawal of clopidogrel is questionable and justified only in order to perform neuraxial anesthesia. More information is needed for patients in dual antiplatelet treatment including prasugrel and tigacrelor.

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