

Is Bleeding the Only Matter of Worry in Clopidogrel Receiving Dental Patients?

Opinion

The population of patients receiving long-term antiplatelet therapy is expanding globally due to the rising prevalence of cardiovascular diseases. Clopidogrel is a thienopyridine antiplatelet drug which is indicated for the prevention of atherosclerotic events such as myocardial infarction, stroke and vascular death. Its active metabolite irreversibly blocks the platelets' P2Y12 receptors and therefore inhibits ADP-induced platelet aggregation. Early worries about management of dental patients receiving clopidogrel focused on possible bleeding complications that may arise after invasive dental treatment and whether a drug holiday is necessary perioperatively. On the other hand temporary withdrawal of clopidogrel has been documented to increase embolic complications. Increasing evidence from clinical studies suggests that high morbidity bleeding complications are uncommon when these patients undergo dental surgery, suggesting that antiplatelet therapy should not be withdrawn perioperatively [1,2]. But should this be the only matter of worry? The expression of the P2Y12 receptor in osteoblasts and osteoclasts has been demonstrated as well [3,4]. Moreover, activation and aggregation of platelets play an important role in bone healing. Platelet releasate (e.g. platelet-derived growth factor [PDGF], vascular endothelial growth factor [VEGF], insulin growth factor-1 [IGF-1], insulin growth factor-2 [IGF-2], epidermal growth factor [EGF], and transforming growth factor- β [TGF- β]) is involved in migration, proliferation and differentiation of progenitor cells that have been attracted in the wound, and also in the inflammatory response to trauma. By these means clopidogrel may have direct and indirect effects in bone healing and remodeling.

The few related studies are still controversial. In 2012, a large scale retrospective cohort study by Jørgensen et al. [5] showed that clopidogrel therapy is associated with increased risk of osteoporotic fractures. They studied 77,503 Danish patients who were prescribed clopidogrel during the years 1996-2008 and 232,510 matched nonusers. They found that patients on clopidogrel therapy had up to 50% increases in risk of osteoporotic fractures (hip, forearm and spine). Interestingly, they also found that subjects with low exposure to clopidogrel (<0.01 defined daily dose) had a lower risk of fracture than nonusers. They hypothesized that this dose-dependent dual effect of clopidogrel may be due to its effects in both osteoblasts and osteoclasts and thereby on both bone formation and resorption.

Syberg et al. [6] found that addition of clopidogrel in osteoblasts' cultures slowed osteoblasts proliferation, decreased cell viability of mature osteoblasts and inhibited mineralised bone nodule formation. These effects were dose-dependent. They also found, using micro-CT, that administration of clopidogrel (1mg/Kg) to rats for one month decreased trabecular bone volume in the

tibia (24%) and femur (18%), and decreased trabecular number (20%). On the contrary, Su et al. [4] evaluated the impact of P2Y12 receptor on osteoclasts' function and pathologic bone loss. They found that mice lacking P2ry12 gene had increased bone mass and decreased serum levels of osteoclast activity marker (CTX). Given this, they administered clopidogrel in mice (30mg/kg) in order to block P2Y12 receptor on osteoclasts and found modest increase in trabecular bone volume compared to vehicle-treated mice.

Yamaguchi et al. [7] investigated the effects of clopidogrel on the prevention of steroid-induced osteonecrosis in rabbits. They administered daily clopidogrel mixed with normal saline in 35 rabbits and only normal saline in other 30 rabbits during four weeks. One week after the initial administration all rabbits were injected once intramuscularly with 20 mg/kg of methylprednisolone acetate. After histopathological examination of femora and humeri they found that the incidence of osteonecrosis in the clopidogrel-treated group (48.5%) was significantly lower than that observed in the control group (73.3%). Finally, Coimbra et al. [8] evaluated the influence of aspirin and clopidogrel in the pathogenesis of experimental periodontitis and periodontal repair in rats. They found, using micro-CT, that clopidogrel (75mg/Kg) had no effect on spontaneous periodontal bone regeneration after two weeks of healing period. In conclusion, these early studies suggest that clopidogrel may have a versatile role in bone healing and remodeling as it regulates platelets' aggregation, and functions of osteoblasts and osteoclasts, through blocking of P2Y12 receptor. Moreover, it is known that many other cardiovascular drugs (b-blockers, statins etc.) may affect bone, and their synergistic or antagonistic effects should be evaluated [9]. Considering the high clinical impact of the subject, clopidogrel's possible role in bone healing and remodeling remains to be elucidated and further research is needed to be contacted.

Opinion

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