Aspirin and Clopidogrel Inhibit Aneurysm Healing after HydroCoil Implantation in External Carotid Artery Aneurysm Model

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Purpose: To understand whether the use of antiplatelet agents leads to less intra-aneurismal tissue formation following coil implantation in a rat end-pouch external carotid artery (ECA) aneurysm model. *Methods:* End-pouch ECA aneurysms were created in adult rats and were then embedded with either platinum or HydroCoils. Rats were treated either with aspirin, clopidogrel, aspirin + clopidogrel, or saline for 2 weeks after coil implantation. At 2 weeks after coil implantation, rats were sacrificed and the aneurysm pouch was removed for histological and immunohistochemical analysis. A blinded single observer calculated the percentage of the organized area and the residual length of elastic lamina within the aneurysm. Student's *t*-test was used to compare data from image analysis between the different groups. *Results:* Within the platinum group, the organized tissue area was not affected by antiplatelet administration (aspirin versus saline, $P = .83$; clopidogrel versus saline, $P = .46$; aspirin + clopidogrel versus saline, $P = .54$). For the HydroCoil group, the organized tissue area was significantly reduced (aspirin versus saline, $P = .02$; clopidogrel versus saline, $P = .04$; aspirin + clopidogrel versus saline, $P = .02$) in rats treated with antiplatelet agents; however, no difference (aspirin versus clopidogrel, $P = .8$; aspirin versus aspirin + clopidogrel, $P = .3$; clopidogrel versus aspirin + clopidogrel, $P = .5$) was found among type or combination of antiplatelets administered. HydroCoil-treated aneurysms had a similar number of macrophages compared to the platinum group ($P = .3819$); however, the HydroCoil group had significant suppression of macrophages in the groups treated with combined antiplatelets ($P = .02$). *Conclusion:* Following HydroCoil implantation, the area of organized tissue is diminished significantly in a rat end-pouch ECA aneurysm model treated with antiplatelets. **Key Words:** Antiplatelet medications—aspirin—clopidogrel—coiling—rat experimental aneurysms.

Introduction

Rupture of cerebral aneurysms leads to subarachnoid hemorrhage and causes significant morbidity and mortality.[1] Urgent treatment of the offending aneurysm is essential in preventing rerupture and further cerebral injury.[2] While microsurgery and clip ligation of the neck of the aneurysm leads to isolation of the aneurysm from the parent vessel, minimally invasive endovascular techniques have become a mainstay, as the International Subarachnoid Aneurysm Trial and the Barrow Ruptured Aneurysm Trial have demonstrated a lower incidence of significant

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Received May 31, 2016; accepted July 1, 2016.

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1052-3057/$ - see front matter

http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2016.07.001

morbidity and mortality in patients who were treated with coil placement versus those treated with surgical clip placement.[3,4] Endovascular techniques have continued to evolve as stents, liquid embolic agents, and flow diverters are showing promise in improving the durability of endovascular treatment of cerebral aneurysms.

Coiled aneurysms undergo thrombosis and subsequently an inflammatory response that leads to permanent fibrosis and healing.[5] To prevent thromboembolic complications after elective coiling, patients are pretreated and maintained on antiplatelet agents such as aspirin and clopidogrel; however, these agents also lead to inhibition of thrombosis and inflammation which prevents aneurysm healing. We aim to understand whether the use of antiplatelet agents leads to inhibition of intraaneurismal tissue formation following coil implantation in a rat arterial aneurysm model.[6-8]

Methods

Animal Preparation and Coil Placement

The protocols for animal use were approved by our University's Committee on the Use and Care of Animals. A total of 40 adult male Sprague-Dawley rats weighing between 350 and 400 g were utilized. Access to food and water was ad libitum. General anesthesia was induced with an intraperitoneal injection of 60 mg/kg sodium pentobarbital (Nembutal; Ovation Pharmaceuticals, Inc., Deerfield, IL) and body temperature was maintained at 37°C with the use of a feedback-controlled heating pad. Under sterile conditions, the bare platinum coils (MicroPlex 18; MicroVention, Inc., Tustin, CA) and hydrogel-coated coils (HydroCoil 14 or 18, MicroVention, Inc.) were cut into 5-mm-long segments.

Once a rat was effectively anesthetized, it was placed in a supine position and the anterior neck region was prepped and draped under a sterile condition. A paramedian incision was then made and blunt/sharp dissection was carried through the fascia and muscle until the carotid sheath was identified. The carotid sheath was opened, leading to the identification and isolation of the internal carotid artery (ICA), external carotid artery (ECA), and common carotid artery (CCA). A permanent ligature was placed 5-7 mm distal to the origin of the ECA using a 6-0 silk suture. A small arteriotomy was made at the site just proximal to the ligature after the proximal blood flow of ECA was controlled by temporary clipping of the CCA and ICA. A 5-mm coil segment (bare platinum coil or HydroCoil) was then inserted into the ECA lumen until the tip of the coil was located at the origin of the ECA. Another ligature was made at the proximal site of the arteriotomy to prevent bleeding and coil migration, and temporary clips at the CCA and ICA were released to restore blood flow. The operative field was inspected to confirm hemostasis and proper location of the coil in the newly created ECA sac. Vasodilation and pulsation of the ECA sac were recognized on removal of the temporary clips, and the wound was closed with 4-0 nylon sutures. Rats were returned to their cages and given access to food and water ad libitum.

Animal Groups

Forty rats were divided into 4 groups depending upon the antiplatelet agents administered to the animals after coil implantation: control saline solution (no antiplatelet medication), aspirin, clopidogrel, or aspirin + clopidogrel. Each of the 4 groups consisted of 10 rats; in each group, 5 rats received bare platinum coil implantation and 5 received HydroCoil implantation. Rats received the antiplatelet medications 2 hours prior to surgical intervention and then once a day for the duration of the 2 weeks. The drug was crushed and mixed into 1 ml saline solution, and the suspension was given to the rats by oral gavage. The dosages of drugs were based on rat weight as follows: aspirin 200 mg/kg or clopidogrel 5 mg/kg.[9] Control rats underwent an identical proce-

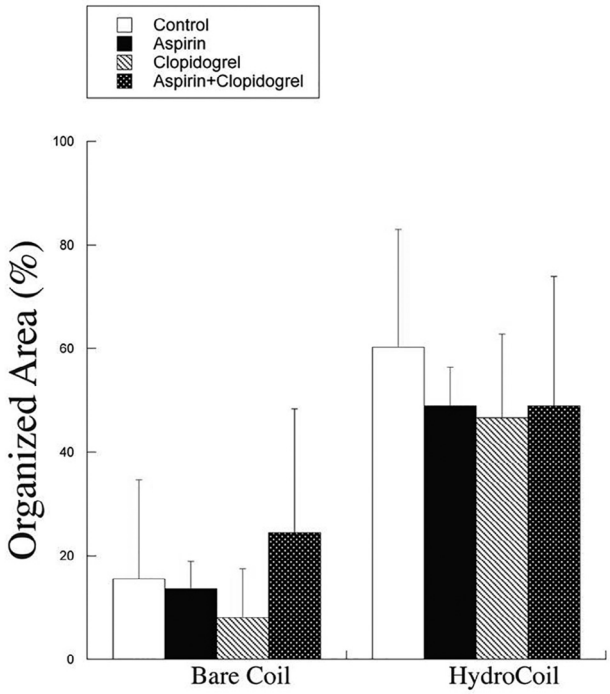

Figure 1. *Percentage of organized tissue area in external carotid artery sacs harvested on day 14 following coil insertion among the different antiplatelet medication groups. Within the bare platinum coil groups (n = 5), the organized tissue area was not affected by antiplatelet administration (aspirin versus saline,* P = *.83; clopidogrel versus saline,* P = *.46; aspirin + clopidogrel versus saline,* P = *.54). For the HydroCoil groups (n = 5), the organized tissue area was significantly reduced (aspirin versus saline,* P = *.02; clopidogrel versus saline,* P = *.04; aspirin + clopidogrel versus saline,* P = *.02) in rats treated with antiplatelet agents; however, no difference was found among type or combination of antiplatelets administered (aspirin versus clopidogrel,* P = *.8; aspirin versus aspirin + clopidogrel,* P = *.3; clopidogrel versus aspirin + clopidogrel,* P = *.5).*