Journal of the Neurological Sciences 339 (2014) 97–101

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

In-vitro thrombogenicity assessment of polymer filament modified and native platinum embolic coils

Gaurav Girdhar [a,*], Megan Read [a], JiHae Sohn [a], Chirag Shah [a], Sanjay Shrivastava [b]

[a] Vascular Therapies Peripheral Vascular, Covidien, 15 Hampshire St., Mansfield, MA 02048, United States
[b] Vascular Therapies Neurovascular, Covidien, 9775 Toledo Way, Irvine, CA 92618, United States

ARTICLE INFO

Article history:
Received 28 August 2013
Received in revised form 28 December 2013
Accepted 22 January 2014
Available online 31 January 2014

Keywords:
Thrombin
Clotting
Embolic
Coils
Fluorogenic
Aneurysm
Intracranial

ABSTRACT

Background: Embolic coils have been used to treat intracranial aneurysms using an endovascular approach for more than two decades. However, significant aneurysm recanalization rates have been reported specifically in large and giant aneurysms. Adding filaments to bare Platinum coils is considered a modification and has been proposed to achieve higher aneurysm occlusion rates as compared to bare Platinum coils. Quantitative information — in terms of thrombin generation potential of these modifications — is however lacking.
Objective: We report here *in vitro* thrombogenicity of Platinum coils containing Nylon (Axium™ MicroFx™ Nylon coil) and PGLA (Axium™ MicroFx™ PGLA coil) filaments and compare them with equivalent bare Platinum Axium™ coils.
Method: We utilize a quantitative method that tracks the formation of thrombin upon exposure of the test samples to human platelet rich plasma using a slow binding fluorogenic substrate.
Results: We report a significant increase in the total thrombin turnover, the peak thrombin amount and the rate of thrombin generation for the Axium™ MicroFx™ coils and filaments compared to the Axium™ coils and Platinum wire.
Conclusion: Nylon and PGLA filaments added to bare Platinum coils increase thrombogenicity of coils. This study offers a robust quantitative method to compare thrombus formation efficacy of embolic coils under static conditions.

1. Introduction

Endovascular embolization using Platinum coils is widely used to treat intracranial aneurysms [1,2]. In spite of its increasing adaptation, significant recanalization rates (25–40%) have been reported specifically for large and giant aneurysms [3–5]. Among various causes of recanalization of aneurysms, insufficient volumetric packing and poor organization of thrombus in the aneurysm sac are notable [6,7]. To overcome these limitations, second generation coils — comprising of a polymer component in the form of a coating or filament added to the bare Platinum coils — have been introduced in the market.

Previous studies have alluded that Nylon filaments added to coils qualitatively shows higher cellular adhesions and interactions with the filaments [8]. A comprehensive matched-pair statistical analysis of filament-containing and bare Platinum coils in clinical use had shown that the former lead to significantly higher occlusion rates (96%) relative to bare or unmodified coils (85%) and do not significantly increase thromboembolic events risk [9]. On the other hand, studies with coated coils have reported insignificant differences or mixed outcome effects over bare Platinum coils in terms of thrombosis and long-term fibrosis [10–12]. Improved thrombosis in filament containing coils provides higher flow resistance (reduced cross-neck flow velocity) imparted by the distribution of filaments in the aneurysm [13]. However, to our knowledge direct quantitative comparisons for thrombin generation potential of such modifications to bare Platinum coils are lacking.

Several methods have been proposed to measure biomaterial contact activation such as chromogenic methods for FXIIa activity measurement, thrombin–antithrombin complex formation, platelet activation marker measurements, fibrinopeptides generation, and microscopy [14–18]. However, these methods do not provide a near real-time history of thrombin generation (the principal enzyme involved in platelet activation and fibrin or clot formation) and as such quantitative thrombogenicity comparisons between products of the same class are lacking. Hemker and colleagues have developed fluorogenic methods that measure the entire course of thrombin generation (designed as a "thrombogram") in clotting - platelet rich or poor - plasma using a slow-binding fluorogenic substrate with added tissue factor (TF) and phospholipids as clotting initiators [19–21]. The methodology has been applied to investigate effects on thrombin generation in plasma due to clotting abnormalities. In

* Corresponding author. Tel.: +1 508 452 1690; fax: +1 508 261 8590.
E-mail address: gaurav.girdhar@covidien.com (G. Girdhar).

0022-510X/$ – see front matter
http://dx.doi.org/10.1016/j.jns.2014.01.030

those applications contact activation is minimized by addition of a contact activation inhibitor (corn trypsin inhibitor) to the test solutions. The methodology has been partially applied for contact activation initiated coagulation for measuring antithrombogenic effects of coatings on catheters [22]. We report here application of this technique for the comparison of prothrombogenic effects of adding filaments to embolic coils having the same metal chassis. Specifically, we demonstrate the reproducibility and feasibility of an in-vitro quantitative method to map the thrombogenicity profiles of three distinct coils tested.

2. Methods

2.1. Coils

The following three unique types of coils manufactured by Covidien (2 mm × 40 mm × 0.29 mm) were tested: Axium™, Axium™ MicroFx™ Nylon, and Axium™ MicroFx™ PGLA. All three types of coils utilized the same metallic chassis made of a Platinum alloy. The only difference was the addition of Nylon or PGLA filaments to the Axium™ MicroFx™ Nylon, and Axium™ MicroFx™ PGLA coils respectively (Fig. 1A). In each experiment, two coils of each type designated above were tested in a 96-well polystyrene microplate as shown in Fig. 1B (*top*). A total of 9 experiments were performed with unique batches of human platelet rich plasma (PRP). Therefore $N = 18$ coils each of Axium™, Axium™ MicroFx™ Nylon, and Axium™ MicroFx™ PGLA, were tested in the study. Wells with no coils added served as the negative control.

2.2. Filaments

The following samples with nominal diameters (mm) as indicated were obtained: PGLA filament (0.023), Nylon filament (0.025), Platinum wire (0.038). For each experiment, the filaments and wire were cut to a length to obtain a total surface area of 0.50 cm^2. A total of 3 experiments corresponding to 3 batches of human PRP were conducted in duplicate for each filament and wire ($N = 6$). Wells with no filaments added served as the negative control.

2.3. Test solutions and experiment

Citrated human PRP was obtained from American Red Cross (Dedham, MA). PRP was centrifuged at 2900 ×*g* to obtain platelet poor plasma (PPP). Platelet count in PRP was adjusted to 2×10^8/mL using PPP. To the diluted PRP, the following reagents were added: a thrombin specific fluorogenic substrate (Z–Gly–Gly–Arg–AMC, Bachem Americas Inc., Torrance, CA) to a final concentration of 400 μM and Calcium Chloride (Sigma Aldrich, St. Louis, MO) to a final concentration of 20 mM. A reference thrombin calibrator solution (Diagnostica Stago Inc., Parsippany, NJ) and 400 μM of the fluorogenic substrate were added to the autologous PPP in separate wells of the microplate for all experiments. 250 μL of test or calibrator solution was added to each well of the microplate and fluorescence was measured in a Synergy™ HT microplate reader (BioTek, VT) with settings: excitation: 360 nm; emission: 460 nm, at intervals of 1 min.

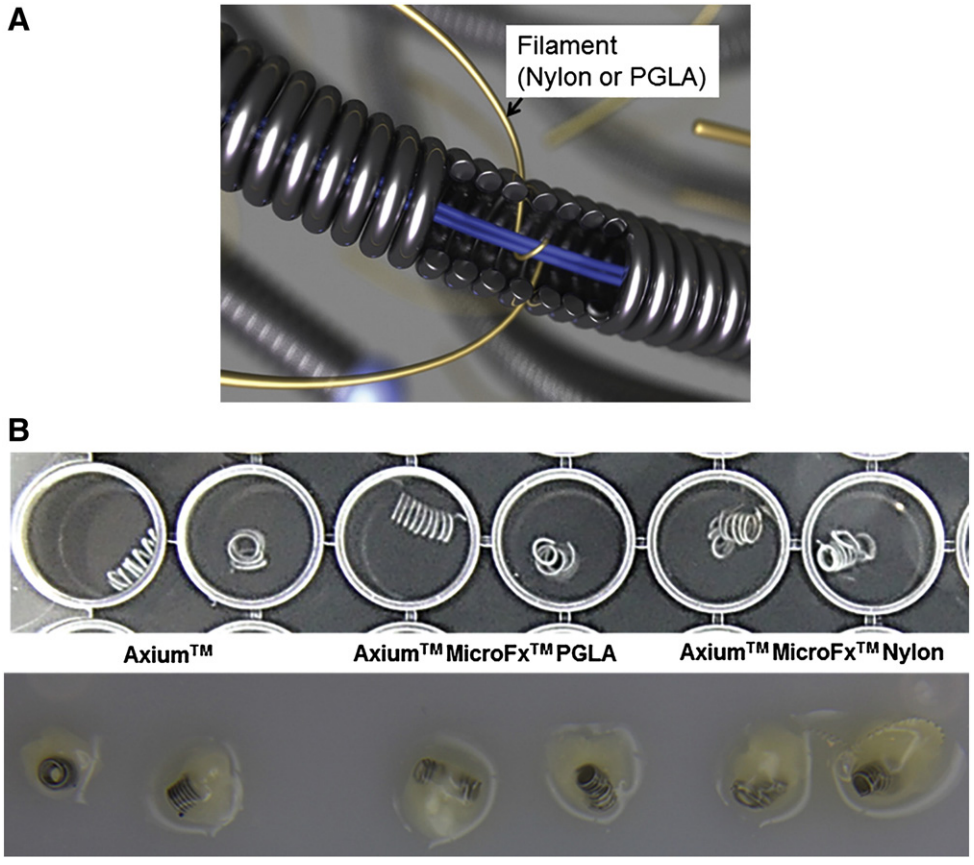

Fig. 1. Axium™ MicroFx™ coil structure and post-experiment thrombus. (A) Schematic view of a typical Axium™ MicroFx™ coil section. All three types of coils utilized the same metallic chassis made of a Platinum alloy. The only difference was the addition of Nylon or PGLA filaments to the Axium™ MicroFx™ Nylon, and Axium™ MicroFx™ PGLA coils. (B) (*top*) Arrangement of coils in the 96-well polystyrene microplate. Coils deployed in a random orientation. (*bottom*) Higher volume of thrombus observed for the filament modified coils at the end of the experiment.