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Bevacizumab and interferon reduce venous recanalization following sclerotherapy☆,☆☆

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ABSTRACT

Purpose: The treatment of venous malformations is difficult because these lesions frequently recur after resection or sclerotherapy. The purpose of this study was to determine whether recanalization of sclerosed venous lumens could be prevented with systemic angiogenic inhibition using bevacizumab or peginterferon alfa-2a.
Methods: To establish an animal model of recanalization of sclerosed facial veins, 18 rabbits had ethanol sclerotherapy of 1 facial vein followed by venography after 4 weeks (n = 6), 12 weeks (n = 6), and 24 weeks (n = 6). Subsequently, 21 different leporids underwent sclerotherapy of both facial veins (n = 42 veins) and were treated pharmacologically in three ways: (1) control (n = 14); bevacizumab (n = 14); or peginterferon alfa-2a (n = 14). Animals received 2 systemic drug doses 1 month prior to and during the procedure. Vessel patency was determined 24 weeks later using venography.
Results: Venous recanalization occurred in 33.3% of sclerosed facial veins after 4 weeks and 50.0% after 12 and 24 weeks. For animals treated with systemic medication, recanalization occurred less frequently when bevacizumab (14.3%, n = 2/14) ($P = 0.04$) or peginterferon alfa-2a (7.7%, n = 1/14) ($P = 0.01$) was administered compared to controls (57.1%, n = 8/14).
Conclusions: Systemic treatment with bevacizumab or peginterferon alfa-2a reduces venous recanalization following sclerotherapy in an animal model. Further studies are indicated to determine whether anti-angiogenic pharmacotherapy can prevent recurrence of venous malformations in humans after sclerotherapy.
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Venous malformations are present at birth and enlarge over time [1–3]. Morbidity includes lowered self-esteem from the deformity, pain, and bleeding. First-line therapy generally is sclerotherapy which involves direct cannulation of the lesion and injection of a sclerosant. Resection is reserved for venous malformations that are localized and can be excised for cure, large deforming lesions, or for symptomatic lesions following sclerotherapy.

The most commonly used sclerosants for venous malformation are ethanol and sodium tetradecyl sulfate (STS). These irritants cause endothelial injury resulting in luminal obliteration because of thrombosis and fibrosis [4]. Therapeutic failure is common because of recanalization of the vessel lumen via thrombus organization and endothelial cell ingrowth [5–11]. We have previously demonstrated diminished recanalization following sclerotherapy by adding autologous fibroblasts to the sclerosant to increase fibrosis [9,10]. We hypothesized that recanalization could be decreased more practically by administering currently available systemic angiogenic inhibitors.

1. Materials and methods

Following approval from the Animal Use and Care Committee at Boston Children's Hospital, 39 New Zealand white rabbits weighing 5 kg were used for two studies: 1) to establish a model for venous recanalization at different time intervals following sclerotherapy (n = 18 rabbits) and 2) to assess the effects of systemic angiogenic inhibition of sclerosed veins using bevacizumab (Avastin; Genentech, Inc., South San Francisco, CA) or peginterferon alfa-2a (PEGASYS; Genentech, Inc., South San Francisco, CA) (n = 21 rabbits).

Facial vein sclerotherapy was performed as described previously [9,10]. A midline cervical incision was made and a segment of facial vein was isolated bilaterally at the junction of the external jugular and facial veins (Fig. 1). Ethanol (0.5 ml) was injected into the lumen of the clamped vein for 10 seconds followed by aspiration and flushing with saline (to minimize the risk of systemic complications). The vein segment remained isolated for 10 minutes and luminal collapse was visually confirmed after removing the clamps.

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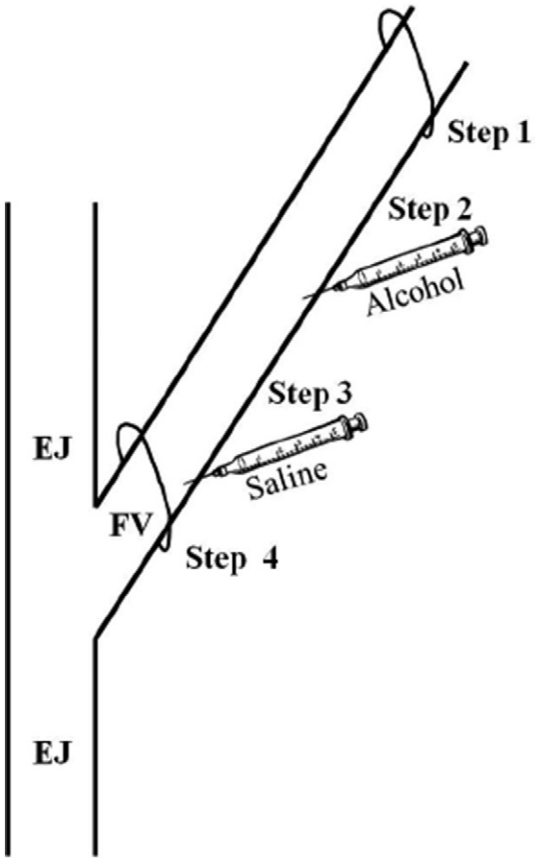

Fig. 1. Sclerotherapy procedure of facial vein (FV). The FV segment is isolated (step 1). Sclerotherapy of the segment is performed by local injection of 0.5 ml of dehydrated alcohol which remains in place for 10 seconds (step 2). The alcohol is then aspirated, and the FV segment is flushed with saline (step 3). The lumen is momentarily filled with blood and reisolated for 10 minutes. Thrombosis is confirmed by visual inspection. The isolated FV segment is returned to normal circulation (step 4). (External jugular vein = EJ).

To establish the time course of vessel recanalization, 18 rabbits underwent sclerotherapy of 1 facial vein (the other vein was untreated) followed by venography at: (1) 4 weeks (n = 6); (2) 12 weeks (n = 6); and (3) 24 weeks (n = 6) [9]. Venography was conducted by dissecting out the bilateral external jugular and facial veins. Direct venipuncture of the external jugular vein (proximal to the facial vein) was performed and iopamidal contrast (3 ml) was injected under fluoroscopy. The sclerosed and contralateral untreated facial veins were assessed for patency. Animals were euthanized following venography.

Twenty-four weeks was established as the end point to assess for venous recanalization in the groups that were to receive pharmacotherapy. Subsequently, 21 leporids underwent ethanol sclerotherapy of both facial veins (n = 42 veins) and were systemically treated with: 1) no medication (n = 14); 2) bevacizumab (n = 14); or peginterferon alfa-2a (n = 14). Drugs were given 1 month prior to sclerotherapy and during their procedure (20 mg of intravenous bevacizumab or 15 mcg of subcutaneous peginterferon alfa-2a) per acceptable weight/sized-based dosing. Venography was performed 24 weeks later.

Data are presented as proportions with 95% confidence intervals (CI). Frequencies were compared using Fisher's exact test. Ninety-five percent CI were constructed using the Newcombe–Wilson method [12,13]. Two-tailed values of $P < 0.05$ were considered significant. Statistical analysis was conducted using the GraphPad Prism version 16.0 (GraphPad Software, Inc., La Jolla, CA).

2. Results

In the model development group of animals, re-establishment of luminal flow occurred in 33.3% (n = 2/6) of sclerosed veins at 4 weeks following sclerotherapy and in 50.0% of veins 12 weeks (n = 3/6) and 24 weeks (n = 3/6) postsclerotherapy. The untreated veins remained patent (n = 18/18) ($P = 0.0003$).

Animals had reduced venous recanalization at 24 weeks if they received bevacizumab (14.3% [95% confidence interval, 4.0–40.0%], n = 2/14) ($P = 0.04$) or peginterferon alfa-2a (7.1% [95% confidence, 1.3–31.5%], n = 1/14) ($P = 0.01$) compared to those that were given no systemic medication (57.1% [95% confidence interval, 32.6–78.6%], n = 8/14) (Figs. 2, 3). Differences in recanalization between bevacizumab and peginterferon alfa-2a were not significant ($P = 1.0$).

One animal in the peginterferon alfa-2a group had delayed wound healing of the cervical incision. The wound had healed by two weeks posttreatment. No additional systemic side effects (e.g., bleeding, evidence of immune dysfunction, infection, intestinal perforation) of bevacizumab or peginterferon alfa-2a were observed in the rabbits.

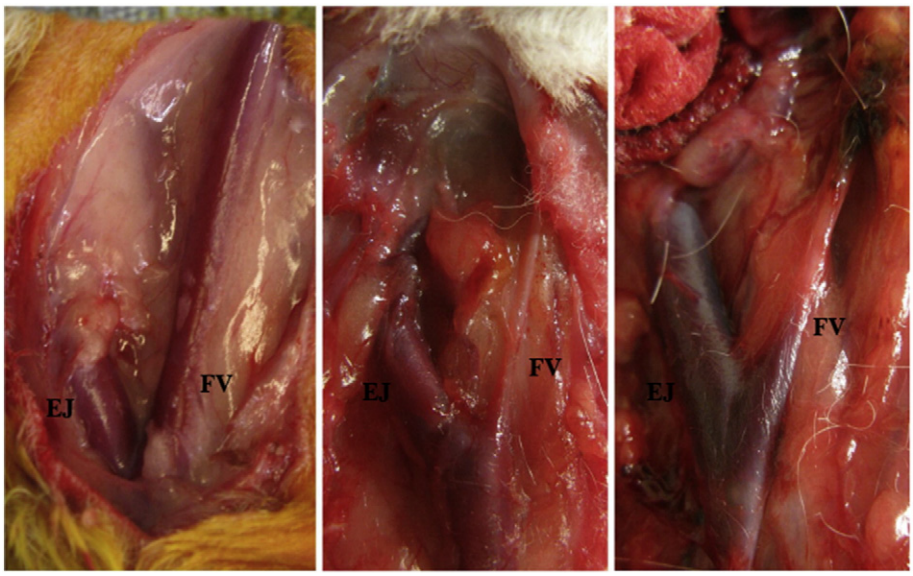

Fig. 2. Rabbit facial vein (FV) segments 24 weeks after sclerotherapy. (Left) FV at bifurcation of external jugular vein (EJ) with patent lumen. (Center) Sclerosed FV segment in bevacizumab group at 24 weeks. The FV is collapsed after sclerotherapy with no flow. (Right) Sclerosed FV segment in peginterferon alfa-2a-treated animal at 24 weeks also exhibits no perfusion through collapsed lumen.

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