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Enhancement of intravascular sclerotherapy by tissue engineering: short-term results

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Abstract

Background/Purpose: Treatment of vascular malformations with sclerotherapy is often complicated by reexpansion secondary to endothelial recanalization. This study examined the use of an autologous fibroblast construct to enhance intraluminal scar formation after sclerotherapy.

Methods: New Zealand rabbits (n = 15) underwent ethanol sclerotherapy of a segment of the facial vein. After intraluminal saline flush, animals were equally divided into 3 groups. In group I, no further manipulations were performed. In groups II and III, collagen hydrogel was injected into the sclerosed vein, respectively, without and seeded with autologous green fluorescent protein–labeled fibroblasts. One week postoperatively, the vein segments were examined for patency and resected for histology.

Results: The sclerosed vein segments remained occluded in all animals. Histological examination of luminal thrombi demonstrated numerous viable fibroblasts in group III, whereas there were none in the control specimens from groups I and II. The presence of the injected autologous green fluorescent protein–labeled fibroblasts within thrombi of group III was confirmed by immunohistochemistry.

Conclusions: An injectable tissue-engineered construct enhances sclerotherapy of the jugular vein in a leporine model by reliably delivering fibroblasts that populate the resultant thrombus. Further analysis of this novel therapeutic concept as a means to augment permanent scar formation and reduce luminal recanalization is warranted.

Venous malformations (VMs), often incorrectly termed "cavernous hemangiomas," are congenital lesions consisting of abnormal venous channels [1-3]. They comprise a wide spectrum of lesions, including simple varicosities and ectasias, discreet spongy masses, and large permeative soft tissue lesions. They can involve any tissue or organ system

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and frequently cross multiple tissue planes [4]. Genetic errors may be responsible for the deficient smooth muscle cells found in the media of involved vessels [1,5,6]. Lesions tend to enlarge slowly, in parallel with normal growth, but can dilate and become symptomatic at any time [7].

Indications for treatment of VM are appearance, pain, functional loss, and bleeding. Treatment options include surgical resection and/or sclerotherapy [8]. Surgery is typically reserved for well-localized lesions but is marked by procedural morbidity and recurrence, especially when performed for complex lesions. Sclerotherapy is based on direct endothelial damage and thrombosis caused by the sclerosing agent. Staged sclerotherapy and occasional embolization of large venous channels can be useful for more complex VM. However, sclerotherapy of VM is also fraught with recurrence [9,10].

Recurrence results from thrombus organization and ingrowth of endothelial cells, leading to recanalization [11-17]. We hypothesized that this process could be prevented by directing this inflammatorylike response toward the induction of local fibrosis through the delivery of autologous fibroblasts. In this study, we examined fibroblast delivery via an injectable tissue-engineered embolus, as a means to enhance short-term vascular sclerotherapy in a rabbit model.

1. Materials and methods

The present study was approved by the Harvard Medical School Standing Committee on Animals under protocol no. 03583.

1.1. Vascular sclerotherapy

New Zealand white rabbits (n = 15) weighing 5 kg were anesthetized with 1% to 5% inhaled isoflurane after induction with ketamine, acepromazine, and buprenorphine injected intramuscularly. Animals received cefazolin intravenously before surgical manipulation. Through a right longitudinal cervicotomy, a 4-cm segment of the right facial vein was temporarily isolated between 2 silk sutures (Fig. 1). Sclerotherapy of the isolated segment was performed by local injection of 0.5 mL of dehydrated alcohol (American Regent Laboratories, Shirley, NY) for 10 seconds. The sclerosing agent was then removed through a 24-gauge catheter, and the vein was flushed with saline. The silk sutures were then momentarily relaxed to allow the lumen to

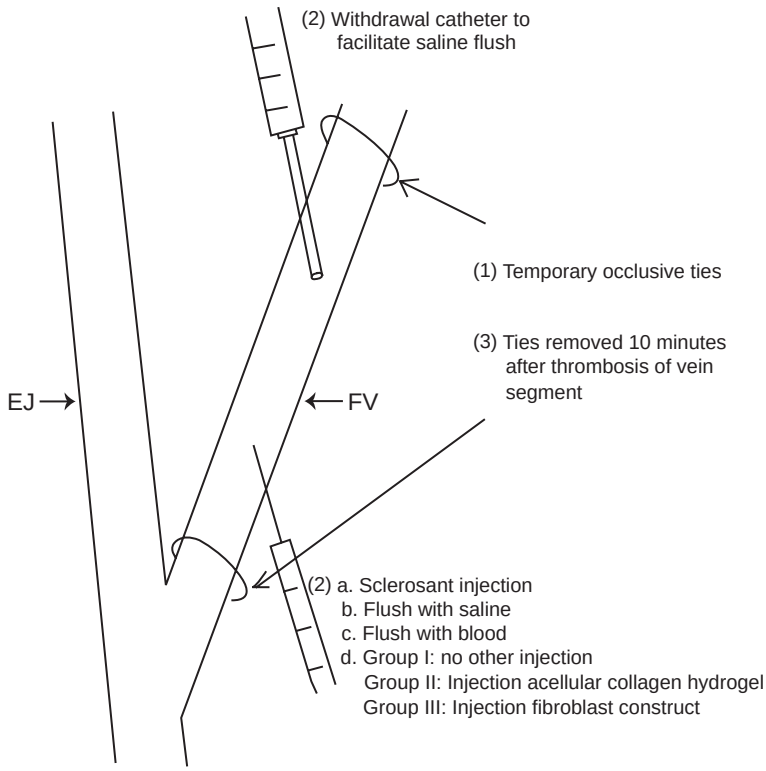

Fig. 1 Right external jugular vein system. Schematic depicts sclerotherapy procedure of facial vein segment. (Step 1) Temporary isolation of vein segment by silk ties. (Step 2) a. Injection 0.5 mL alcohol. b. Saline flush of sclerosed lumen facilitated by withdrawal catheter. c. Silk tie momentarily relaxed to flush sclerosed lumen with blood. d. Group I, No other injection; group II, injection 0.5-mL acellular collagen hydrogel; group III, injection 0.5-mL collagen hydrogel seeded with autologous fibroblasts. (Step 3) Temporary sutures isolating vein segment were removed 10 minutes after thrombosis confirmed by visual inspection. EJ indicates external jugular vein; FV, facial vein).