VEGF Modified Fibrin Biomatrix Improves Wound Healing Following Severe Tissue Ischemia

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Introduction
Local delivery of growth factors supporting wound healing is discussed to be superior to systemic administration. As local reservoir several scaffolds including fibrin have been shown promise for sustained local stimulus of targeted cells via locally released growth factors and cytokines. Studies have suggested that vascular endothelial growth factor (VEGF) is a regulator of physiologic and pathologic angiogenesis and is known to physiologically bind to fibrin.

Materials and Methods
In the current study we evaluated the efficacy of sprayed fibrin biomatrix modified by increasing rhVEGF_{165} concentrations in the potential of reducing tissue necrosis following severe ischemia in a rodent flap model. After flap harvesting the recipient sites were randomly assigned to sprayed fibrin biomatrix without or supplemented with VEGF_{165} at 20, 200, 400, and 800 ng/mL final fibrin clot. Quilting sutures served as controls. Necrotic flap tissue was documented by digital photography over a 1 week period and quantified using planimetric analysis. Flap perfusion was measured using a 2D laser Doppler imaging system. This system allows detecting superficial tissue perfusion using a non contact laser which generates a color coded image. Immunohistochemical means (vWF and sma) were used to determine impact on angiogenesis.

Results
Flap necrosis on day 3 as well as on day 7 was significantly less in the groups having VEGF_{165} at 200 and 400 ng/mL final fibrin clot as compared to the control group (Fig. 1). The fibrin biomatrix by itself had also trend wise less necrotic areas than the control group. Significantly improved flap perfusion was also found in the 200 and 400 ng/mL VEGF/FS group compared to control (Fig. 2). Determining the ratio between sma and vWF positive stained vessels as a marker for functional angiogenesis it was found that 20 and 200 ng VEGF165/mL final fibrin clot significantly increased the amount of functional vessels when compared to the control group.

![Fig. 1. Flap necrosis assessed by planimetric measurement. *# p < 0.05 vs control](image)

![Fig. 2. Representative 2D laser Doppler images of the control and VEGF165 supplemented fibrin biomatrix group (blue/low, red/high perfusion).](image)

Discussion and Conclusions
In summary, we found that flap necrosis was substantially reduced and flap perfusion significantly increased when using sprayed fibrin biomatrix with VEGF in a dose dependent manner partly via induction of functional angiogenesis.

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