Journal of Cranio-Maxillo-Facial Surgery 43 (2015) 1028–1032

Contents lists available at ScienceDirect

Journal of Cranio-Maxillo-Facial Surgery

journal homepage: www.jcmfs.com

Axially vascularised mandibular constructs: Is it time for a clinical trial?

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ARTICLE INFO

Article history:
Paper received 20 April 2014
Accepted 21 October 2014
Available online 29 October 2014

Keywords:
Mandibular reconstruction
Tissue engineering
Regenerative medicine
Axial vascularization
Arterio-venous loop
Clinical trials

ABSTRACT

Applying regenerative therapies in the field of cranio-maxillofacial reconstruction has now become a daily practice. However, regeneration of challenging or irradiated bone defects following head and neck cancer is still far beyond clinical application. As the key factor for sound regeneration is the development of an adequate vascular supply for the construct, the current modalities using extrinsic vascularization are incapable of regenerating such complex defects. Our group has recently introduced the intrinsic axial vascularization technique to regenerate mandibular defects using the arteriovenous loop (AVL). The technique has shown promising results in terms of efficient vascularization and bone regeneration at the preclinical level.

In this article, we have conducted a narrative literature review about using the AVL to vascularize tissue-engineering constructs at the preclinical level. We have also conducted a systematic literature review about applying the technique of axial vascularization in the field of craniofacial regeneration.

The versatility of the technique and the possible challenges are discussed, and a suggested protocol for the first clinical trial applying the AVL technique for mandibular reconstruction is also presented.

1. Introduction

1.1. Why axial vascularization?

Applying principles of regenerative medicine in the field of cranio-maxillofacial reconstruction has now become a daily practice. The wide spectrum of applications ranges from the simple addition of bioactive bone fillers to much more sophisticated techniques for bone replacement and reconstruction (Sandor et al., 2013). Indications have included reconstruction after minor developmental defects, trauma, infections, benign cysts, or tumours, but seldom after malignant tumour excision (Clokie and Sandor, 2008; Trautvetter et al., 2011; Schuckert et al., 2009). Warnke et al. (2004), who used a completely different technique from those used in the previous case reports, reported the only published case of regeneration after cancer ablation. The main technical difference was related to vascularization of the regenerated tissue.

Although all of the reported cases for mandibular regeneration used the conventional extrinsic vascularization strategy, in which the constructs were left to acquire a parasitic blood supply from the recipient site of implantation, Warnke et al. (2004) used an ***axial vascularization*** strategy through a prelamination procedure in the Latissimus Dorsi (LD) muscle followed by free tissue transfer of the regenerated mandible. Although this technique avoided bony donor site morbidities, the need to harvest the LD muscle represented a major drawback of this prelamination technique. This single case report highlighted the need for an efficiently vascularized construct if the regenerative therapy is to be applied after cancer ablation.

Reconstruction after cancer ablation usually requires a large volume of tissue to be implanted in an area of deficient vascularity due to extensive resection and perioperative irradiation. In a recent meta-analysis published in 2014, grafted bone combined with radiotherapy was identified as a negative prognostic factor for

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http://dx.doi.org/10.1016/j.jcms.2014.10.018
1010-5182/

implant survival (Schiegnitz et al., 2014). Growth factors such as VEGF (Vascular Endothelial Growth factor), TGF-β1 (Transforming Growth factor), or BMP (Bone Morphogenic Protein) or compounds such as deferoxamine were brought into the defects in experimental animals and have improved bone repair in irradiated areas (Ehrhart et al., 2005; Kaigler et al., 2006; Farberg et al., 2012); however, the regeneration of a complex critical size defect in an irradiated field has not been demonstrated. Furthermore, milligram dosages of growth factors that may be needed to optimize vascularization and bone formation are extremely expensive, and thus are impractical for clinical applications. To the best of our knowledge, all of the trials to regenerate irradiated bony defects are still at the preclinical level. We believe that axial vascularization would be the only clinically oriented technique capable of vascularizing large defects in such complex situations.

1.2. Prelamination or prefabrication?

Axial vascularization of scaffolds aims at providing the construct with blood supply through a defined and dedicated vascular axis. In this context the blood supply of the construct is not randomly acquired from the implantation site, and thus implantation in an area of low vascularization potential, as in irradiated or fibrosed surgical sites, may be possible (Kneser et al., 2006). The two major techniques for axial vascularization are prelamination and prefabrication.

Prefabrication of a tissue construct is done simply by implanting an arterio-venous fistula or loop (AVL) or a vascular pedicle underneath or within the construct. This results in spontaneous sprouting of vessels from the loop or pedicle and subsequent revascularization of the whole tissue construct (Erol and Spira, 1979; Morrison et al., 1990; Guo and Pribaz, 2009). Prelamination is another technique introduced by Pribaz and Fine (1994) in 1994, in which the implantation of a construct into a vascularized territory (flap) is performed to create a customized vascularized unit. The end result of both techniques is an axially vascularized unit that depends for its nourishment on a defined vascular axis (Fig. 1).

Two more important terms to mention in this context are 'intrinsic' and 'extrinsic' vascularization modes. The extrinsic vascularization of a construct denotes acquiring its blood supply from the periphery towards the centre, whereas the intrinsic vascularization mode denotes that the core region of the construct is being vascularized first (Lokmic and Mitchell, 2008). Accordingly, prefabrication is considered an intrinsic axial vascularization strategy. The construct in prelamination, however, is extrinsically vascularized within an intrinsically vascularized territory (Eweida et al., 2012) (Fig. 1).

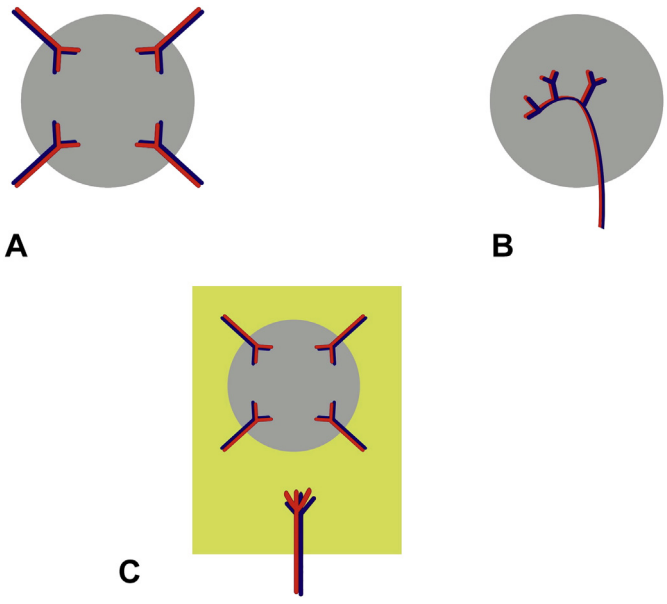

Fig. 1. Diagrammatic illustration of vascularization strategies. A: Extrinsic vascularization of a construct, B: Intrinsic vascularization, C: Prelamination technique.

As the reconstruction of challenging or irradiated bone defects requires an axially vascularized tissue bulk, applying the prelamination strategy will invariably result in remarkable donor site morbidity where the whole vascularized territory (mostly a muscle flap) has to be transferred to the recipient site (Warnke et al., 2004; Mesimaki et al., 2009). The prefabrication technique, however, when applied to a tissue construct, entails only the transfer of this construct with its pedicle, thus diminishing donor site morbidity to the minimum. Moreover, the prefabrication technique could be applied at the recipient site as a primary reconstruction technique, avoiding donor site morbidity completely (Horch et al., 2014; Eweida et al., 2014).

One of the most extensively investigated techniques to induce axial vascularization in the tissue constructs is the AVL or fistula (Horch et al., 2012; Arkudas et al., 2013, 2007; Horch et al., 2013; Bitto et al., 2013), and its superiority over the vascular bundle in terms of vascular density and tissue regeneration potential has been clearly demonstrated (Tanaka et al., 2003).

The aim of this article is to present a comprehensive review of literature about using the technique of axial vascularization in bone regeneration, especially for mandibular reconstruction. We also discuss the versatility of the technique and the challenges facing the first clinical trial for mandibular reconstruction using the AVL.

2. Material and methods

We have conducted a narrative literature review of the application of the AVL to vascularize tissue-engineered constructs at the preclinical level.

We have also conducted a systematic literature review on applying the technique of axial vascularization of tissue constructs in the field of craniofacial regeneration. An Internet search was performed among the articles published on PubMed in English or German language using the following string: ("Bone Growth" OR "Bone Formation" OR "Tissue Engineering") AND ("Mandible" OR "Maxilla" OR "Mandibular reconstruction" OR "Maxillary reconstruction") with activated filters of "Article type" and "Species" to "Case reports" and "Humans" respectively. Exclusion criteria were as follows: reports of spontaneous bone regeneration, ridge augmentation, distraction osteogenesis, and bone regeneration with random vascularization.

3. Results

3.1. The AVL model from 'Thought' to 'Goat'

The first documented idea for axial vascularization using the AVL was described by Erol and Spira (1979) in 1979 in a rat model. Morrison et al. further developed the model and inserted the loop into isolation chambers (Mian et al., 2000; Hofer et al., 2003). They successfully demonstrated the induction of vascularization in polymer and gel matrices (Cassell et al., 2001). Since 2006, the design and characterization of the isolation chambers and the inset of the AVL were further developed by the work of Horch et al. (Kneser et al., 2006), in which the engineering of vascularized transplantable bone was first successfully demonstrated by this research group (Fig. 2).