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Experimental Study of the Effect of Lyophilized Platelet Growth Factors on Healing of Critical Size Defect in Craniofacial Bone

Thesis

Submitted for Partial Fulfillment of M.D. Degree in Plastic, burn and maxillofacial surgery

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List of Abbreviations

Abb.	Full term
ADSCs	Adipocytes derived stem cells
AP	Activator protein
BMPs	Bone morphogenetic proteins
b-TCP	B-tricalcium phosphate
CARE	Committee on Animal Research and Ethics
CSD	Critical size defect
DBM	Demineralized bone matrix
EGF	Epidermal growth factor
FBS	Fetal bovine serum
FGF	Fibroblast growth factor)
GFs	Growth factors
IGF	Insulin-like growth factor
LPGFS	Lyophilized platelet growth factors
MOBL	Mesenchymal osteoblasts
MSCs	Mesenchymal stem cells
Ob	Osteoblasts
Oc	Osteocytes
OCL	Osteoclasts
PC	Platelet concentrate
PGFs	Platelet growth factors
PLGA	Polylactic-co-glycolic acid
PTHrP	Parathyroid hormone-related protein
rhPDGFBB	Recombinant human PDGF-BB
TGF-β	Transforming growth factor-β
VEGF	Vascular endothelial growth factor

ABSTRACT

Background: The maxillofacial trauma and their complications represent a great socio-economic concern for the Egyptian health system. There are multiple reconstructive options are available for reconstructing the critical size defects in craniomaxillofacial field. The reconstruction of the critical sized defects by autografts is considered the golden standard. They offer minimum immunological rejection, complete histocompatibility and can provide the best osteoinductive, osteoconductive and osteogenicproperties. With the continued growth of cell therapy applications being used in clinical medicine and within operative plastic and reconstructive surgery, there remains continued interest in using a variety of easily accessible methods for regenerative medicine efforts. Growth factors derived from platelet rich plasma (PRP) can contribute to tissue regeneration in allogenic bone graft, by assisting cell migration, proliferation, differentiation and extra cellular matrix synthesis.

Objective: To study the effect of human lyophilized GFs on healing of critical size bone defect in craniofacial bone of animal.

Materials and Methods: This study was conducted between October 2016 and October 2018. It was conducted at the Medical Research Center associated with Ain Shams Faculty of Medicine and approved from the Research Ethics Committee (REC) of Faculty of Medicine, Ain Shams University (No: FMASU 1969/2014). Using 30 albino rats divided into 3 groups .

Results: The results obtained in this study revealed a statistically significant bone healing after reconstruction of critical size calvarial bone defects by Lyophilized platelet growth factors (LPDGF) seeded on allogenic Demineralized bone matrix (DBM). In conclusion, this study presents a beneficial method for reconstruction of critical size calvarial bone defects by an already made non-immunogenic new tissue regenerate.

Conclusion: This study advocate the use of DBM with LPDGF as a reconstructive tool for bone regeneration. But further clinical studies are needed to evaluate its rule in the unfavorable general and local conditions.

Keywords: Lyophilized platelet growth factors , critical size defect , demineralized bone matrix

INTRODUCTION

Bone defects caused by trauma, tumor resection, pathologic degeneration and congenital malformations is a challenging. Reconstruction of critical-sized bone loss has a significant clinical problem in craniofacial surgery and requires application of adjuncts such as bone grafts to accelerate bone regeneration and fracture healing ***(Feighan et al., 1995).***

According to ***Mabrouk et al. (2014)*** the maxillofacial trauma and its complications represent a great socio-economic concern for the Egyptian health system.

There are multiple reconstructive options are available for reconstructing the critical size defects in craniomaxillofacial field.

In 2005, over 2.2 million bone grafting procedures were performed by orthopedists, neurosurgeons, dentists, and plastic surgeons worldwide ***(Giannoudis et al., 2005).***

Currently, critical-size bone and soft-tissue defects are reconstructed using a variety of autogenous bone, alloplastic implants, composite free flaps, and rigid fixation devices ***(Valerio et al., 2014).***

The reconstruction of the critical sized defects by autografts is considered the golden standard. They offer minimum immunological rejection, complete histocompatibility

and can provide the best osteoinductive, osteoconductive and osteogenic properties ***(Samartzis et al., 2005)***. The limitations in using autografts are the limited graft availability, bone resorption and the need for an additional surgery with resulting donor site morbidity ***(Pollock et al., 2008).***

Composite vascularized free flaps may fail secondary to infection, extrusion and microsurgical complication resulting in removal and return to a deteriorating wound bed. Although vascularized composite allotransplantation has gained momentum clinically, a lifelong postoperative course of immunosuppression has been associated with significant morbidity and mortality ***(Manassero et al., 2013).***

With the continued growth of cell therapy applications being used in clinical medicine and within operative plastic and reconstructive surgery, there remains continued interest in using a variety of easily accessible methods for regenerative medicine efforts ***(Hu et al., 2015).***

Allogenic Demineralized bone matrix (DBM) is a form of allograft bone prepared by decalcifying the allogenic bone while preserving the extracellular matrix. This process is called demineralization ***(Biswas et al., 2010)***. This technique destroys the antigenic surface structure of the bone. Therefore, DBM does not evoke any appreciable local foreign body immunogenic reaction. DBM has the same properties of allograft in carrying the osteoconductive potential ***(Katz et al., 2009)***.

Numerous therapies based on osteoinductive growth factors have been developed to reduce the need for autogenous bone, As is evident by proteomics and functional analyses, human platelets contain a myriad of molecules exhibiting important physiological functions ***(Maguire et al., 2003).***

These include the GFs (growth factors) that are stored in the α-granules. PGFs (platelet growth factors) include three PDGF (platelet derived growth factor) isoforms (PDGF-AA, -AB and -BB), VEGF (vascular endothelial growth factor), TGF-β (transforming growth factor-β; TGF-β1 and TGF-β2), EGF (epidermal growth factor), FGF (fibroblast growth factor) and some IGF(insulin-like growth factor).There is increasing interest in the use of human PGFs both as therapeutic biological products in the field of regenerative medicine as well as for various applications in cell cultures and cell therapy as a replacement of FBS (fetal bovine serum). Such preparations need, however, to be standardized ***(Blairet al., 2009).***

For such clinical applications, a single-donor PC (platelet concentrate), or a platelet-rich-plasma donation, of autologous or allogeneic origin, is used as a topical product, as such or after activation by exogenous thrombin to induce the release and temporary entrapment of the GF into a fibrin-rich biomaterial, called platelet gel. The GF-rich fraction can be applied on tissues, either alone or in combination with a carrier, such as collagen or ceramics ***(Marx et al., 1998).***

Currently, the major therapeutic applications of platelet lysates rich in GF are to stimulate bone regeneration in oral, maxillofacial, plastic and orthopaedic surgery, or to accelerate wound healing of soft tissues ***(Borzini et al., 2005).***