Applicability of Homologous Fibrin Sealant in Bone Repair: An integrative Review

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Abstract—The repairing of bone defects is still a challenge for researchers and clinicians. Nonetheless there are many procedures that use different biomaterials such as scaffolds for bone regeneration however the results are often still unsatisfactory. As a result, the fibrin sealant derived from the interaction between proteins participating in the final blood coagulation cascade, is one of the most promising biopolymers in the tissue engineering field due to its unique characteristics. The present study aimed to perform a systematic review on homologous fibrin sealants highlighting its applicability as a three-dimensional framework in the process of bone regeneration. The database used for search strategy was the PubMed (Medline) and followed the guidelines provided in the PRISMA statement. From an initial 313 articles, only 12 articles between 2009 to 2019 were selected for this review after checking all inclusion and exclusion criterias. Due to this background, it is notable that fibrin sealant is one of the promising biopolymers used for tissue engineering and bone regeneration applications.

Keywords—Fibrin Sealant, Bone Repair, Tissue engineering, Biopolymer, Scaffold.

I. INTRODUCTION

Bone is a highly dynamic tissue that undergoes a continuous renovation process to maintain its architectural bone structure, mechanical properties and metabolic capacities and when injured is able to reestablish the lost tissue morphofunctional characteristics without compromising the function (SEAL; OTERO; PANITCH, 2001; LOI et al., 2017).

However, this mechanism may or may not occur in large defects, such as tumor resections, unconsolidated fractures, congenital malformations, and the loss or surgical removal of bone fragments (HONMA et al., 2008; SPICER et al., 2012; HETTIARATCHI et al., 2017), in addition, it may require reconstructive operative procedures whose bone grafting is the main treatment technique (POUNTOS; GIANNNOUDIS, 2016; BAI et al., 2018).

Among the available bone grafts, the autograft is still considered the gold standard in the bone regeneration techniques because it has osteogenic, osteoinductive and osteoconductive properties combined. Although its use is associated with limited supply, possible complications in the donor site and the unpredictability of bone resorption, which may negatively influence postoperative outcomes (POLLOCK et al., 2008; PILIPCHUK et al., 2015).

Because of these limitations, research is being conducted in order to a new treatment approach for bone regeneration, aiming at the development of biologically active natural materials (GHIASI et al., 2017).

As a result, the fibrin sealant derived from the interaction between proteins participating in the final blood coagulation cascade, is one of the most promising biopolymers in the tissue engineering field due to its unique characteristics (NOORI et al., 2017).

For instance, its excellent biocompatibility, controllable biodegradability, and multi-functional three-dimensional structure that provides support, cell proliferation and differentiation, anchoring surrounded molecules and growth factors and therapeutic agents transport, makes fibrin sealants have remarkable advantages over other biomaterials, besides a candidate
with potential to assist in engineering of bone tissue (SHIU et al., 2014; SPOTNITZ, 2014; BORIE et al., 2015).

Although, all fibrin sealants contain fibrinogen and thrombin, qualitatively and quantitatively the exact composition varies, such as the velocity of rate of hemostasis, clot biochemistry, viscosity, adhesive strength, durability, fibrin polymerization rate and the three-dimensional structure of the clot, and can directly influence its use (WOZNIAK, 2003; DIETRICH et al., 2013; CUNHA et al., 2015). For this purpose, the present study aimed to perform a systematic review on homologous fibrin sealants highlighting its applicability as a three-dimensional framework in the bone regeneration process.

II. MATERIALS AND METHODS

This review followed the guidelines provided in the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). Medical subject heading (MeSH) terms were used in this study. The database used for search strategy was the PubMed (Medline). The search string used was following these terms “fibrin sealant AND bone repair”.

It has been included all articles in English at periods between 2009 and 2019, with access to the full text, either openly or by signatures available at the University of São Paulo (Brazil).

The titles and abstracts of the articles were evaluated and those that did not meet each inclusion criteria were removed from the review. After second analysis, only articles that used fibrin sealant as a three-dimensional scaffold for the lodging of biologically active cells and molecules in the bone regeneration process were selected for detailed review.

Inclusion Criteria:

- Periods between 2009 – 2019;
- Articles types: full articles available;
- English language;
- In vivo research model;
- Fibrin sealant used as a scaffold for tissue engineering applications.

Exclusion Criteria:

- Any article that did not meet the inclusion criteria listed earlier.

![Fig.1: PubMed (Medline) Keywords combination](image-url)
III. RESULTS

In total, from an initial 313 articles, only 12 articles were selected for this review (see Table 1) after checking all criteria listed earlier such as periods between 2009 to 2019, full articles available, English language, fibrin sealant used as a scaffold for tissue engineering and in vivo research model. For full search process see Fig. 1.

Table 1 Summaries of the selected articles about tissue engineering applications of fibrin scaffolds.

| Author (Date)          | Objective                                                                 | Component origin and/or Trade name | Implantation Site                  | Mixture with biomaterials or cells          | Conclusion                                                                 |
|------------------------|---------------------------------------------------------------------------|------------------------------------|------------------------------------|--------------------------------------------|---------------------------------------------------------------------------|
| McDuffee et al. (2012) | To compare the efficacy of osteoprogenitors in fibrin glue to fibrin glue alone in bone healing of surgically induced ostectomies of the fourth metacarpal bones in an equine model. | Homologous (non-commercial)        | Metacarpal bone in horses           | Osteoprogenitor cells or fibrin sealant alone | Injection of periosteal-derived osteoprogenitors in a fibrin glue carrier into surgically created ostectomies of MC4 does not accelerate bone healing. |
| Reppenhagen et al. (2012) | To assess the safety and efficiency of a bone substitute as an alternative for autologous bone in the treatment of benign bone tumours and tumour-like lesions. | Homologous Tissucol™ Duo S         | Distal tibia; calcaneal; glenoid in human | Biphasic calcium phosphate granules          | The biomaterial represents an easy-to-handle alternative to autologous cancellous bone grafts for the treatment of benign bone tumours and tumour-like lesions. |
| Zhang et al. (2012)    | To clarify whether it could be efficient to reconstruct the alveolar bone by the combination of bone marrow stem cells (BMSCs) without pre-osteoinduction in vitro with fibrin glue (FG). | Homologous (non-commercial)        | Rat alveolar bone                  | Bone marrow stem cells                      | The results suggest that the strategy of combing BMSCs with FG is effective in the repair of alveolar bone defects. Its clinical application is promising. |
| Streckbein et al. (2013) | To evaluate the efficacy of bioactive implants (ADSC in fibrin glue) for repair of critical-size mandibular defects in athymic rats. | Homologous Beriplast™ P            | Mandibular defects in rats         | Adipose-derived stem cells                  | Fibrin sealant is a suitable biological scaffold for cell transplantation. |
| Xuan et al. (2014)     | To compare the potentials of PRF-mixed Bio-Oss® and Tissell®-mixed Bio-Oss® to enhance bone regeneration in | Tissell™                           | Canine sinus model.                | Demineralized bovine bone                   | The findings from this study suggest that when platelet-rich fibrin is used as an adjunct to Bio-Oss® particles for bone augmentation |
| Author (Date) | Objective | Component origin and/or Trade name | Implantation Site | Mixture with biomaterials or cells | Conclusion |
|--------------|-----------|-----------------------------------|-------------------|------------------------------------|------------|
| Lappalainen et al. (2015) | To evaluate ossification of cranial bone defects comparing the healing of a single piece of autogenous calvarial bone representing a bone flap as in cranioplasty compared to particulated bone slurry with and without fibrin glue to represent bone collected during cranioplasty. | Tisseel™ | Rabbit calvarial | Autologous particulate bone | Autogenous bone grafts in various forms such as solid bone flaps or particulated bone treated with fibrin glue were associated with bone healing which was superior to the empty control defects. |
| Santos et al. (2015) | To compare the potential of bone repair of collagen sponge with fibrin glue in a rat calvarial defect model. | Tissucol™ | Rat calvaria | Fibrin sealant alone | Results have shown the benefits of using collagen sponge and fibrin glue to promote new bone formation in rat calvarial bone defects, the latter being discreetly more advantageous. |
| Zazgyva et al. (2015) | To establish an experimental model and assesses the effect of glass granules fixed with fibrin compared to fibrin alone as fillers of the osteochondral defects created in the weight-bearing and partial weight-bearing regions of the distal femur in six adult rabbits. | Tisseel™ Lyo | Rabbit distal femur | Bioactive glasses | A commercially available fibrin sealant can be successfully used to retain bioactive glass granules in the defects, offering a fast intra-operative and a subsequently stable fixation. |
| Hao et al. (2016) | To evaluate the efficacy of local injection of bone mesenchymal stem cells (BMSCs) and fibrin glue in the | Homologous (non-commercial) | Rat distal femur | Allogeneic bone mesenchymal stem cells | The analyzes demonstrated that local injection of BMSCs-seeded fibrin glue promoted |
| Author (Date)            | Objective                                                                 | Component origin and/or Trade name | Implantation Site | Mixture with biomaterials or cells | Conclusion                                                                                          |
|-------------------------|---------------------------------------------------------------------------|------------------------------------|-------------------|------------------------------------|-------------------------------------------------------------------------------------------------------|
| treatment of atrophic nonunion in an animal model. |                                                                                                        |                                    |                                 |                                                                                                       |
| **Mehrabani et al. (2018)** | To investigate the healing and regenerative effects of fibrin glue associated with adipose-derived stem cells (ADSCs) and fibrin glue scaffold alone with autologous bone grafts in experimental mandibular defects of the rabbit. | Autologous                         | Rabbit mandible    | Adipose-derived stem cells         | The healing process had a significant increase in the thickness of new cortical bone when fibrin glue scaffold associated with Adipose-derived stem cells was used. |
| **Pomini et al. (2019)**  | To evaluate the support system formed by a xenograft fibrin sealant associated with photobiomodulation therapy of critical defects in rat calvaria. | Tisseel® Lyo                       | Rat calvaria       | Demineralized bovine bone          | The support system formed by the xenograft fibrin sealant associated with the photobiomodulation therapy protocol had a positive effect on the bone repair process. |
| **Rezaei et al. (2019)**  | To evaluate the effects of PRP and canine BM-MSCs (marrow-derived mesenchymal stem cells - cBM-MSCs) in combination with a suitable carrier (fibrin glue) on periodontal regeneration. | Autologous                          | Dog class II furcation defects | PRP, cBM-MSCs and alone           | More studies should be done in order to recommend an effective therapeutic approach that induces endogenous regenerative processes, such as cell homing. |
IV. DISCUSSION

The aim of the present study was to perform a systematic review of the homologous fibrin sealants unique properties as a support material for cell adhesion, migration, proliferation and differentiation, and to enhance the physical and biological osteoconductive biomaterials properties.

The advances achieved in reconstructive surgical techniques combined with the development and natural biopolymers improvement by tissue engineering have attracted the attention of several research groups because it is a promising alternative to existing treatments (CHEN; LIU, 2016).

Among the available sealants, fibrin sealants are the most promising in this field due to the combination of excellent biocompatibility, biodegradability and intrinsic bioactivity. Additionally, over the last few decades emphasis has been placed on the importance of fibrin sealant properties in the repair of bone defects in different anatomical regions (NOORI et al., 2017).

As a consequence, it has been searched for alternative methods to obtain blood components, for this reason, a group of researchers from Center for the Study of Venoms and Venomous Animals (CEVAP-Unesp-Botucatu-SP-Brazil) has developed a fibrin adhesive derived from the snake Crotalus durissus terrificus venom and the buffalo blood. In its composition, the cryoprecipitate containing fibrinogen and coagulation factors are derived from the buffalo blood (Bubalus bubalis), and the functional thrombin by gyroxin, a thrombin-like protein derived from the snake (FERREIRA, 2014; BISCOLA et al., 2017; FERREIRA et al., 2017; MOZAFARI et al., 2018).

Likewise, fibrin biopolymer is a clinically useful tool due to flexibility and applications diversity such as nerve injury repair, chronic ulcer treatment, and bone repair (BUCHAIM et al., 2015, 2016, 2017; DE OLIVEIRA GONÇALVES et al., 2016; ROSSO et al., 2017).

Hence several studies have been reported the use of fibrin sealants as a support for mesenchymal stromal cells (MSCs) and stem cells derived from adipose tissue to facilitate cell attachment, growth and differentiation, allowing enhancements of expansion and survival in the area implanted (RYU et al., 2005; KALBERRATTEN et al., 2008; VADALÀ et al., 2008).

In the same time, the insertion of these cells into the three-dimensional fibrin network has presented promising results in the process of bone repair in several models (ZHANG et al., 2012; STRECKBEIN et al., 2013; HAO et al., 2016; MEHRABANI et al., 2018; REZAEI et al., 2019). In addition, these researchers suggested that fibrin sealant is able to lead a stemcells microenvironment, without deforming its structure, increasing cell survival time and therefore being effective in repairing bone defects.

However, previous results from McDuffee et al. (2012) contradict the previously mentioned results, since they affirm that osteoprogenitor cells inserted in the three-dimensional network formed by fibrin sealant is not able to accelerate the process of bone consolidation.

Despite, the fibrin sealants have beneficial characteristics in the bone regeneration, it is still not possible to have precise control over the microarchitecture of these materials and good tensile strength (GUÉHENNEC; LAYROLLE; DACULSI, 2004). Consequently, is necessary to associate with materials that have great scaffolding potential in many tissue engineering applications in order to minimize or eliminate these limitations. In this way, it allows the manufacture of multifunctional scaffolds with greater resistance mechanics, the graft greater stability in the surgical site, and longer time of cellular support throughout the process of bone repair (AHMED; DARE; HINCKE, 2008).

Several experimental and clinical trials have demonstrated the synergistic characteristics of fibrin sealant associated with materials that have great scaffolding potential led to satisfactory results (REPPENHAGEN et al., 2012; XUAN et al., 2014; LAPPALAINEN et al., 2015; ZAZGYVA et al., 2015; POMINI et al., 2019).

V. CONCLUSION

Due to this background, it is notable that fibrin sealant is one of the promising biopolymers used for tissue engineering and bone regeneration applications. Indeed, the combination with different types of bone grafts, biomolecules and stem cells make this scaffold unique and attractive feature for futures studies.

Nevertheless, there is a necessity for additional studies, for evaluation the concentrations of the components, as a fibrinogen and thrombin, which directly interfere in the density of the network, allowing or not the cellular migration and consequently the bone consolidation.

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