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Adhesives for treatment of bone fractures: a review of the state-of-the art

Abstract

Treatment of fractures remains challenging and carries a high economical burden to both patients and society. In order to prevent some of the complications, the use of bone adhesives has been proposed, but up to date, bone adhesives are not part of the current clinical practice. Early results of use of bone cements and bone glues are promising, focusing in the areas of highly fragmented fractures, fixation of long bone fractures, filling bone voids and defects, promoting osseointegration, preventing non-union while maintaining the reduction of fracture fixation. This review aims to describe the state-of-the-art of the development, properties and use of adhesives in fracture treatment.

Key words

Fracture treatment; bone adhesives; bone cements; bone glues, fracture reduction

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All the authors declare no conflict of interest in regard to the content of this manuscript.

Introduction

In England alone, the risk of hospital admission for fracture has been calculated to be 47.84 per 10,000 population [1], with the number of fractures increasing as the age increases and the bone quality decreases. The economic burden is not only associated with hospitalization costs, but also have societal impact with mean associated costs calculated up to US$12,500 in 2005 [2]. Especially, non-unions have a high financial impact, with average direct costs of treatment of an established long bone non-union to be as high as US$11,333 and £29,204, in USA and UK respectively [3]. On a "best case scenario", the costs were found to be £15,566, £17,200 and £16,330 for humeral, femoral, and tibial non-unions respectively [4].

Bone healing is a delicate, yet complex process, where the synergy of mechanical stability with biological factors is critical [5]. The mechanical environment of fracture healing is addressed with the use of metallic implants, mainly plate and screw constructs or intramedullary nails, depending on the fracture location and type [6]. The biological component involves the interaction of osteogenic cells, growth factors, osteoconductive matrix and angiogenesis [5]. When there is lack of biological factors, then surgeons introduce them, in the form of autologous bone graft, progenitor cells and growth factors [7,8]. The existence of optimum mechanical and biological factors leads to better surgical outcomes [9].

An impaired fracture healing process can be associated with several predisposing factors which can be summarised as patient and injury related and surgeon related (outcome of treatment) [10]. Fixation of fractures can be challenging since unreduced fractures and residual fracture gaps can increase the risk of non-union [10]. Not surprisingly therefore, lately, a lot of interest has been generated to develop bone adhesives, materials able to bind bone surfaces together, withstand the loads at the fracture gaps, while allowing the biological factors of bone healing to take place and gradually degrade leaving room for bone ingrowth.

Currently, medical adhesives are used to improve wound healing and implant anchorage in hard tissue. The main types of adhesives are fibrin glue, or cyanoacrylates, also known as bone cement. Bone glues are not yet popular in current practice for gluing together two bone surfaces, because of certain limitations. Interestingly, fibrin glue is not strong to support the load in the fracture gap, while it degrades quickly in a wet environment [11]. On the other hand, bone cement is not considered biocompatible, with studies suggesting having toxic effect in bone, while it degrades too slowly, if any at all [12].

The aim of the herein study is to investigate the current state of the art of bone adhesives, in order to understand how close to clinical practice bone glue might be. The main objectives are to identify the

main materials used, their area of application, the existing evidence supporting their use, and their main strengths and weaknesses.

Materials and Methods

A Pubmed search was performed up to 1st of April 2020, with key words “bone cements”, “bone glue” and “bone adhesives”, incorporating the following script: ("bone cements"[Pharmacological Action] OR "bone cements"[MeSH Terms] OR ("bone"[All Fields] AND "cements"[All Fields]) OR "bone cements"[All Fields] OR ("bone"[All Fields] AND "glue"[All Fields]) OR "bone glue"[All Fields]) AND (("bone and bones"[MeSH Terms] OR ("bone"[All Fields] AND "bones"[All Fields]) OR "bone and bones"[All Fields] OR "bone"[All Fields]) AND ("adhesives"[Pharmacological Action] OR "adhesives"[MeSH Terms] OR "adhesives"[All Fields])).

Articles were included based on the following criteria:

a) Use of bone adhesives
b) Application in bone fracture treatment
c) English language for both abstract and manuscript

The following information was collected from the articles:

- Adhesive material used, including product name for the commercially available adhesives
- Application, e.g. fixing fractures, maintaining reduction, improve bone regeneration, providing mechanical support and adhesion
- Type of study (laboratory characterization, ex vivo or cell study, animal model, clinical study)
- Main outcome

Exclusion criteria were articles published in other than English language, articles focusing on soft-tissue adhesives and glues for implant anchorage, and articles not specifying the clinical application of the bio glues.

Results

The search resulted in 236 titles, out of which 198 were in English. Reviewing titles and excluding topics on soft tissue glues or applications irrelevant to trauma and orthopaedics, the articles left were 113. After reviewing the abstracts, 58 articles were left, out of which after carefully reading and reviewing the full text, 23 articles met the inclusion criteria and formed the basis of this work [11–33] (see Figure 1).

The majority of the papers concerned *ex vivo*, cell or animal studies, with only two studies taking place in a clinical environment

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Materials

In the studies collected, two main types of bone adhesives were found; bone cements and bio-glues. Bone cements were mostly phosphate [13,14,25], polyalkenoate [28,29] or acrylate-based cement [12,15,16,30–33], either alone or with the addition of fillers, to improve their properties. Types of glues used were fibrin glue [17–20], consisted of human fibrinogen, bovine thrombin and calcium chloride, and dental adhesives of different consistencies [15,21,22,33], but also bioinspired glues [23,24,26]. Common filers were phosphoserine [13,24,25], in an attempt to manufacture a bioinspired glue, calcium [13,15,20,25,30,32] and magnesium [14], as natural elements providing stability and biocompatibility, glass [21,28,29], to provide increased compressive strength, and growth factors, such as platelet rich plasma, to improve bone regeneration [11,19,26,27].

Applications

Medical glues have the potential of being used in different applications, from wound healing and controlling hemostasis, to bond tissues together, but could also act as carriers for growth factors and surfaces for tissue regeneration. Overall, the following applications for fracture treatment were identified:

(a) Treatment of highly fragmented fractures [13,16]
(b) Fixation of long bone fractures [14,15,21,22,25,30–32]
(c) Filling bone voids and defects [15,19,20,27–29,32]
(d) Promoting bone regeneration [11,12,27]
(e) Preventing non-union [30]
(f) Maintaining reduction of fracture fixation [17,18,26]

Cytotoxicity and Biocompatibility

One of the main aspects of biomaterial development is to ensure that the biomaterial is non toxic to cells and animals, prior to human use. Following this, many studies have included cytotoxicity and animal toxicity assays, along with testing the adhesive properties of the new bioadhesives. Cyanoacrylate-based cements were thought to be toxic, but fewer toxic effects were seem when longer-

chain cyanoacrylates were used [12]. On the other hand, phosphate based cements were non toxic to both cells and animals [13]. Generally, bioinspired glues were the most cyto- and bio-compatible when compared to cement effects [16,24,26].

Controllable Degradation

Adhesives glues and cements focus on maintaining the bone fragments glued together, while allowing bone to regenerate. In order for bone to substitute the bioadhesive, the biomaterial has to degrade in a controllable manner. From the studies included here, it seems that the addition of fillers inhibits rapid degradation. Especially, adding calcium demonstrated to regulate degradation in a steady rate [25,32], but this was also possible when plasma rich plasma was used with fibrin glue [26].

Adhesion strength

One of the most important properties that a bone glue should have, must be the ability to bond wet bone surfaces together, and maintain the adhesion in time. Phosphate cements [25], bioinspired glues [24], dental adhesives with fillers [16,21] had increased adhesive strengths, while growth factor-rich adhesives and acrylate-based cements were capable of holding wet bone fragments in vivo [15,26].

Compressive and tensile loads

Cements were able to withstand higher compressive loads, which were further increased with the addition of fillers [14,15,25,28,29,32]. When tensile testing was performed, then cements were strong [31] [33], but also adhesives and bioglues had high shear bonds [11,22].

Promoting bone regeneration

Cements with calcium fillers were found to improve bone union [30] and cell proliferation [32]. Fibrin glue alone had negative effect on bone regeneration, but the addition of either plasma rich plasma or calcium seemed to overcome this hurdle, and actually promote bone regeneration [19,20]. Bioinspired glues, even when the glue structure was not permeable, allowed bone healing [23]. In general, addition of growth factors and mesenchymal stem cells had a positive effect in cell proliferation, differentiation and attachment [11,26,27].

Setting/Operating time

Operating time was not widely checked in the studies included in this review. However, addition of fillers lead to decrease of setting time [29], while a use of bioadhesive in a clinical setting resulted in a shortened operation time [17]. When dental adhesives were used, setting was controlled via light-curing of the adhesives, using dental blue light [15,33].

Complications

Apart from two articles which used bioglues in a clinical setting [17,18], the rest of the papers investigated the properties of bone adhesives in either *in vitro* or *in vivo* settings. In the clinical papers, neither complications nor side effects were discussed, while no cases of allergic reactions to bioglues were reported.

In the rest of the manuscripts, only in the case of bone cements, inflammation was observed in histopathological analysis [12]. However, when longer-chain cyanoacrylates were used, inflammation signs were decreased [12]. Interestingly, where it was provided, histology showed no signs of inflammation [13,16,24,26].

Discussion

Bone adhesives could be ideal biomaterials to keep bone surfaces together, while slowly degrading in vivo. Especially, bone glues will aim to treat fractures in low-bearing bones, by reducing fractures and maintain fracture reduction. In the case of bone voids, bone adhesives could temporarily fill the gap until bone regeneration takes place. Last but not least, adhesives with fillers, such as growth factors, could promote osseointegration and osteogenesis in compromised cases.

Currently, the use of bioadhesives is not part of the modern clinical practice to treat fractures. The studies included in this report were either in a laboratory or preclinical stage, or in a small clinical study, without medium- or long-term results. Some studies used bone cements, currently used in fixing implants in bone, to glue together bone fragments [11–14,23,27–33]. The rest of the studies were focusing in bio-inspired glues, using natural components, such as fibrinogen, thrombin, chitosan or platelet rich plasma [13,15–22,24,33]. Addition of fillers looks to be a very popular technique, in order to manipulate the properties of either bone cements or bioadhesives, especially in addressing weak mechanical properties or providing growth factors to improve bone regeneration.

Bone cements show promising results in terms of adhesion to wet bone surfaces and sustaining high compression and tensile stresses. However, it has been shown that cements have toxic effects in vitro and in vivo [12]. On the other hand, natural or bioinspired glues may not cause toxicity, but their compression and adhesion strengths are smaller than those of bone cement. One other important topic is the degradability of bioadhesives, in synergy with bone regeneration, ensuring that the bone fragments are always in contact, and glue part being replaced by new bone. Altogether, bone regeneration of bioadhesives has not fully described, as not all bioadhesives have been implanted in animal model. This means that up to now, there is no bioadhesive that is safe enough for clinical use and on the same time provide adequate mechanical stability for fracture healing.

At this point, what is missing is a bioglue that combines mechanical strength and adhesive bonds on wet surfaces, with ability to promote bone regeneration while degrade in a controllable way. It appears

that the toxicity of bone cements remains an issue of concern, so a new bioadhesive, based on natural components should be the way to go forwards. The novel bioadhesive should be cyto- and bio-compatible, able to withstand high compressive and tensile stresses, while strongly adhere to wet bone surfaces. Meanwhile, in the body, it should slowly degrade, leaving room for the newly formed bone. Moreover, one could argue that if growth factors and osteogenic cells are included in the bioadhesive formulation , even in compromised cases, the probability of delayed union, malunion or non-union will be small. In addition to all the above-mentioned properties, bioadhesives should be easy to prepare and apply, ideally reducing the operative time.

In conclusion, based on the findings of this study, bone adhesives show promising outcomes in maintaining reduction, fracture fixation and promoting osseointegration. However, up-to-date there is no product that possesses all of the above mentioned desirable properties. Additionally, no systematic use of bone glues has been established as yet in the clinical setting. It is anticipated that ongoing research in this area will continue and in the non- too long future, the ideal adhesive material will be developed to fulfil the clinical gap that exists.

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