Journal section: Biomaterials and Bioengineering In Dentistry
Publication Types: Review
doi:10.4317/medoral.16.e115
http://dx.doi.org/doi:10.4317/medoral.16.e115

The use of hydrogels in bone-tissue engineering

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Received: 27-02-2010
Accepted: 23-04-2010

Park JB. The use of hydrogels in bone-tissue engineering. Med Oral Patol Oral Cir Bucal. 2011 Jan 1;16 (1):e115-8.
http://www.medicinaoral.com/medoralfree01/v16i1/medoralv16i1p115.pdf

Article Number: 16888 http://www.medicinaoral.com/

eMail: medicina@medicinaoral.com
Indexed in:
Science Citation Index Expanded
Journal Citation Reports
Index Medicus, MEDLINE, PubMed
Scopus, Embase and Emcare
Indice Médico Español

Abstract

Many different types of scaffold materials have been used for tissue engineering applications, and hydrogels form one group of materials that have been used in a wide variety of applications. Hydrogels are hydrophilic polymer networks and they represent an important class of biomaterials in biotechnology and medicine because many hydrogels exhibit excellent biocompatibility with minimal inflammatory responses and tissue damage. Many studies have demonstrated the use of hydrogels in bone-tissue engineering applications. In this report, the summary was conducted on various kinds of polymers and different modification methods of hydrogels to enhance bone formation.

The results revealed that hydrogels are applied for bone regeneration and that the modification of hydrogels with bioactive molecules or cell-based approaches resulted in significant increases in new bone formation. This suggests that the use of hydrogels with modification may offer an option for bone-tissue engineering, and further research is needed to identify the biological and physical properties of hydrogels.

Key words: *Hydrogel, polymer, bone, growth factor, cell.*

Introduction

Many different types of scaffold materials have been used for tissue engineering applications, and hydrogels form one group of materials that have been used in a wide variety of applications (1). A gel is defined as a three-dimensional network swollen by a solvent, and hydrogels are hydrophilic polymer networks that may absorb from 10-20%, up to thousands of times their dry weight in water, and this property allows the cells to adhere, proliferate, and differentiate onto the hydrogels (2).

Hydrogels represent an important class of biomaterials in biotechnology and medicine because many of them exhibit excellent biocompatibility with minimal inflammatory responses and tissue damage, and thus many studies on bone-tissue engineering applications have been undertaken (3-6). In this report, the summary was conducted on various kinds of polymers and different modification methods of hydrogels in bone regeneration applications.

Material and Methods

A Medline search (PubMed) was conducted, and works published in the English language from 2000 up to and including July 2009 were included in the review. The

following search terms were used in different combinations: "hydrogel," "polymer," "bone," "growth factor," and "cell."

Meta-analysis was performed if the following criteria were met. All studies involving the bone repair or bone regeneration having both test and control groups were considered. An outcome measurement of histologic evaluation with histomorphometric analysis or radiographic evaluation with relative density had to be reported. Mean and standard deviation values of newly formed bone or radiographic density from each study were used, and weighted mean values were assessed to account for the difference in the number of subjects between the different studies. To compare the results between the test and control groups, the log odds ratio in mean and 95% confidence intervals (CI) were calculated. All analyses were performed using Comprehensive Meta Analysis, version 2.0 (Biostat, Englewood, NJ, USA).

This review will include polymer type, characteristics of hydrogels, *in vitro studies, and in vivo experiments.*

Results and Discussion

Methodological Quality

Most of the studies reported only in vitro results. Several studies included results from in vivo experiments. However, there were only a few randomized controlled clinical trials and case series performed on patients using hydrogel applications (7).

Type of Polymer

Hydrogels can be formed using natural materials, synthetic materials, or some combination of the two (1). Various natural biomaterials, including alginate, hyaluronic acid, collagen, fibrin and agarose, and synthetic polymers, such as poly(ethylene glycol) and poly(ethylene glycol) fumarate have been employed for the preparation of hydrogel scaffolds (8). Hydrogel materials must be biocompatible and have non-toxic degradation products, and they should have sufficient mechanical properties and promote cell attachment and tissue formation (9).

Gelation time

Controlling the gelation time is important, especially when the gel is formed in vivo, as this allows an effective entrapment of biologically active additives, such as growth factors and cells at the site of application (10). Gelation can be controlled by changing pH or temperature or addition of additives (11). Photopolymerization is an attractive technique, because the gelation occurs rapidly, under physiological temperature, with minimal heat production and controllable space and time characteristics (12).

Degradation

Gel matrix may be reabsorbed by simple dissolution, hydrolysis, or enzymatic hydrolysis (10). Space is needed for the tissue to form. Thus, diffusion of collagen and subsequent mineralization are limited in non-degradable networks, resulting in limited tissue formation (9). The degradation rate of the hydrogels may be controlled by the different polymer and the amount of cross-linking molecules in the network. Hydrogels that degrade in a manner which matches the rate of new bone formation may be optimal for bone-tissue engineering (3). For polymeric degradation products, kidney filtration molecular weight cut-off and possible accumulation of high molecular weight degradation products in the reticuloendothelial system have to be considered when applying the polymer scaffolds (10).

Mechanical strength

Hydrogel scaffolds are also being used in the field of bone-tissue engineering, especially in non-load bearing areas (13). Various initial concentrations and the length of the macromer influence the overall cross-linking density of the network, resulting in different mechanical properties (9).

Mechanical properties may be increased by combining the hydrogels with the particles of ceramic materials, such as β-tricalcium phosphate, hydroxyapatite, demineralized bone matrix, or calcium carbonate (14,15). The introduction of hydroxyapatite was found to improve not only the mechanical and cell-attachment properties of the alginate scaffolds, but also the activity and viability of cells cultured on composites (14). The microcarriers may serve as appropriate cellular anchors, and it was reported that they provided cell-adhesive sites with biochemical improvements (6).

Modification with biologically active additives

Hydrogel-forming polymers can be tailored to exhibit biochemical, cellular, and physical stimuli that guide cellular processes, including cell migration, proliferation, and differentiation (Table 1) (12). Biologically active additives have been added to the hydrogels, including bone morphogenic protein (BMP) and fibroblast growth factor (FGF) (16,17). Gradual release of the growth factor was continued for at least 14 days when it was incorporated into gelatin hydrogel.

Small molecules can be diffused very rapidly, and the small molecules may be conjugated to the polymer to control the release profile (5). Attempts have been made to covalently incorporate cell membrane receptor peptide ligands within the hydrogel matrix to stimulate adhesion, spreading, and growth of cells (18). One of the most commonly researched adhesive peptides, Arg-Gly-Asp (RGD), showed no detrimental effect on the viability of encapsulated cells, and a much higher density of attached cells was seen with the RGD-modified hydrogels (9). BMP-2 was conjugated to the hydrogels, including substrates for matrix metalloproteinase, acting as linkers between the synthetic polymer chains (17), and the synthetic peptide derived from BMP was

Table 1. Different methods of modifying the hydrogel.

Type	Modification	Reference
Conjugation	Arg-Gly-Asp (RGD)	(17)
Conjugation	Bone morphogenetic protein-2 (BMP-2) derived peptide,	(4)
Conjugation	Fluvastatin	(5)
Loading	Mesenchymal stem cell	(11)
Loading	Osteoblast	(6)
Loading	Bone morphogenetic protein	(17)
Loading	Fibroblast growth factor	(16)
Scaffold	Hydroxyapatite	(14)
Scaffold	β-tricalcium phosphate	(15)

conjugated to the alginate gel to apply for the bone defects (19).

Cell-based approach

Hydrogels can be utilized as cell immobilization matrices to produce various biological products, such as proteins, and to recreate the environments for the damaged or lost tissues (13). Scaffolds designed to encapsulate cells must be capable of being gelled without damaging the cells, and must be nontoxic to the loaded cells (2). These hydrogels should allow permeation of biologic medium nutrients to promote cell proliferation and/or induce cell differentiation (8).

An increase in macromer concentration may lead to a more highly cross-linked network with higher mechanical strength. However, an increase in radical concentration during polymerization may lead to transport limitations for nutrients and oxygen to the encapsulated cells. Further, it was shown that lower initial viability was seen with a higher macromer concentration (2,9).

A trend of decreasing viability was seen after a couple of weeks in in vitro cultures, and this decrease may have been partially attributable to the newly produced extracellular matrix components from the encapsulated cells (9). It was also noted that hydrogels with greater swelling showed higher differentiation of mesenchymal stem cells (MSCs) than those that swelled less.

The effects of hydrogels in in vivo models

Many studies have demonstrated the bone-promoting effect of local application with different hydrogels in various animal models (3,17,19). It was shown that when bone-marrow stromal cells were implanted into tibial bone defects along with alginate gel particles, they spontaneously differentiated into osteoblasts (19). Application of the gelatin hydrogel-connective tissue growth factor complex, together with a collagen scaffold to the bone defect in a rat femur, was reported to result in remarkable induction of osteoblastic mineralization markers and distinct enhancement of bone regeneration (20). It was noted that recombinant human BMP-2-loaded synthetic hydrogels, including substrates for matrix metalloproteinase acting as linkers, were remodeled into bony tissue when the gels were implanted into critical-size defects in rat crania (17).

Differences in log odd ratio of regenerated bone between modified and unmodified groups from meta analysis and their 95% CI were 4.5 and 3.5-5.6 (Fig. 1). These numbers revealed that modification of hydrogels with bioactive molecules or cell-based approaches resulted in significant increases in new bone formation.

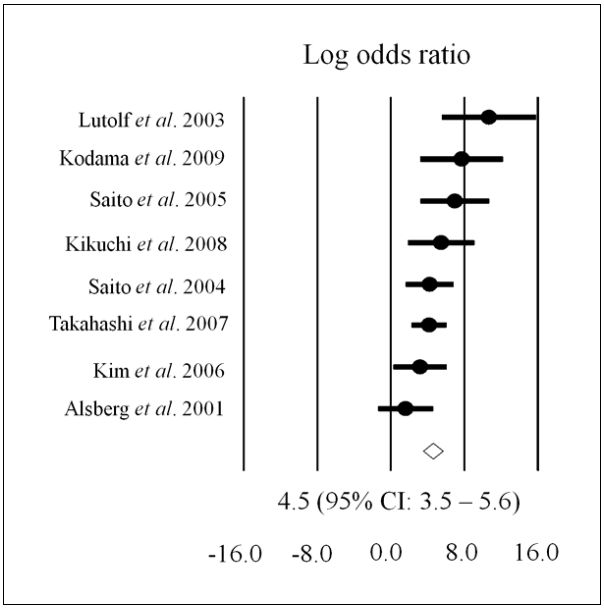

Fig. 1. Differences in log odd ratio of regenerated bone between modified and unmodified groups from meta analysis and their 95 % confidence intervals (95% CI).

Conclusions

In this report, a summary was conducted on various kinds of polymers and different modification methods of hydrogels to enhance bone formation. The results revealed that hydrogels are applied for bone regeneration and that the modification of hydrogels with bioactive molecules or cell-based approaches resulted in significant increases in new bone formation. This suggests that the use of hydrogels may offer an option for bone-tissue engineering, and further research is needed to identify the biological and physical properties of hydrogels.

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