ISSN NO. 2320-5407

Journal homepage: http://www.journalijar.com
Journal DOI: 10.21474/IJAR01

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH

RESEARCH ARTICLE

THE ANTI-BACTERIAL ACTIVITY OF BIOACTIVE GLASS.

A.TRISHALA[1], Dr.CAROLINE JACOB[2]

1. A.Trishala, Ist BDS, Saveetha Dental College and Hospitals, Saveetha University, Chennai.
2. Dr.Caroline Jacob, Senior Lecturer, Department of periodontics, Saveetha Dental College and Hospitals, Saveetha University, Chennai.

Manuscript Info

Manuscript History:

Received: 11 April 2016
Final Accepted: 13 May 2016
Published Online: June 2016

Key words:
bioactive glass, antibacterial property, periodontal disease, periodontal therapy.

Corresponding Author

A.TRISHALA.

Abstract

Aim:- To evaluate data regarding the anti-bacterial activity of bio-glass with emphasis on its mechanism of action and future directions in periodontal therapy.

Objective:- Bioactive glasses have always been considered as practical bone substitute materials. Recent data has brought to light an important characteristic which is its antibacterial action. This article overviews the properties of bioactive glasses and their applications, with special mention of their anti-bacterial activity.

Background:- Bioactive glasses are novel dental materials. Bioactive glasses are composed of calcium and phosphate which are present in a proportion that is similar to bone hydroxyapatite. These glasses bind to the tissue and are biocompatible. They have a wide range of medical and dental applications and are currently used as bone grafts, scaffolds and as coating material for dental implants.

Reason:- Bone grafts currently require adjunctive antibiotic therapy when placed in a defect site. Bio-active glass been has shown to have an inherent anti- bacterial property that may prove to be advantageous in regenerative periodontal therapy.

Introduction:-

Periodontitis is an inflammatory disease that affects the tissues that surround and support the teeth. Periodontal disease involves progressive loss of the alveolar bone around the teeth, and if left untreated, can lead to the loosening and subsequent loss of teeth as a result of alveolar bone destruction[1]. In order to replace or regenerate affected alveolar bone, a wide range of regenerative graft materials have been devised. Bioactive glasses (BAG) are one such group of bio-materials which are used in the fields of dentistry and orthopaedics to repair or replace damaged bone[2]. A material is said to be bioactive, if it gives an appropriate biological response and results in the formation of a bond between the material and the tissue[3]. Bioactive glasses are composed of calcium and phosphate which are proportionally similar to the hydroxyapatite present within the bone[4]. They also have the unique ability to dissolve in biological fluids and release ions such as silica, sodium and calcium. This ionic dissolution facilitates hydroxyapatite formation and direct bonding to bone and soft tissues[5]. In addition, the quick dissolution with rapid change in pH of the surrounding medium enables these glasses to exhibit anti-bacterial properties[6]. They have a wide range of medical and dental applications and are currently used as bone grafts[3], scaffolds[7] and coating material for dental implants[3].

Various Forms of Bioactive Glasses:-

S.No.	Bioactive Glass	Chemical Composition
1)	45S5 - Bioglass (US Biomaterials Corporation, FL, USA)	46.1 mol% SiO_2, 26.9 mol% CaO, 24.4 mol% Na_2O and 2.5 mol% P_2O_5.
2)	58S	60 mol% SiO_2, 36 mol% CaO and 4 mol%. P_2O_5
3)	70S30C	70 mol% SiO_2, 30 mol% CaO.
4)	S53P4- BonAlive (Biomaterials Ltd. - Finland)	53 mol% SiO_2, 23 mol% Na_2O, 20 mol% CaO and 4 mol% P_2O_5.

Processing of bioactive glasses:-

Commercially produced bioactive glasses are produced using conventional glass powder manufacturing methods which include melting and quenching. Producing bioactive glasses by conventional glass technology is expensive as it requires high temperature[3]. Low-temperature sol-gel processing offers a favorable alternative to conventional glass processing, which considerably reduces the costs due to lower processing temperatures[3]. Sol-gel derived bioactive glasses also exhibit highest specific surface area, high osteoconductive properties and a significant degradability[8].

Types of BAG:

S.No	Brand	Active Components	Information	Applications	Advantages	Disadvantages
1)	NovaMin® (Glaxo SmithKline - London, UK)	Calcium sodium phosphosilicate (chemical formula: $CaNaO_6PSi$) ,45% SiO_2, 24.5% Na_2O, 24.5% CaO and 6% P_2O_5.	Delivers silica and ionic calcium, phosphorus, and sodium, which are necessary for bone and tooth mineralization.	To treat dentin hypersensitivity and the remineralisation of teeth.	NovaMin® prevents demineralization and aids in remineralization.	Apatite formation and blocking of the dentine tubules may take several weeks and do not provide immediate relief.
2)	BonAlive® bioactive glass S53P4 (BonAlive Biomaterials Ltd. - Finland)	SiO_2 53%, Na_2O 23%, CaO 20%, P_2O_5 4%.	BAG in contact with tissue fluid develops a silica-gel layer on the glass surface. This allows calcium phosphate (CaP) precipitation which crystallizes to a HA surface and enables bonding of the BAG to the surrounding bone.	Used as a bone graft in cranio-maxillofacial and orthopaedic surgeries.	BonAlive has one of the highest bacterial growth inhibitory effect.	-

3)	BioGran® (Zimmer Biomet company - USA)	Cefadroxil, 45% SiO_2, 24.5% Na_2O, 24.5% CaO and 6% P_2O_5.	Biogran is a resorbable, synthetic bone-graft material consisting of an internal silica gel surrounded by a calcium phosphate shell. Phagocytes enter through cracks in the outer shell and remove the silica core. A calcium phosphate hollow bone growth chamber is formed, which enables the osteoprogenitor cells to differentiate into osteoblasts and lay down bone in the center of the Biogran Granule. Bone tissue then grows from granule to granule.	It is used as bone grafts.	Biogran is an effective treatment for oral bone defects. The bone restored with Biogran was maintained for a longer period.	-
4)	PerioGlas® (Block Drug Co., NJ, USA)	45% SiO_2, 24.5% Na_2O, 24.5% CaO and 6% P_2O_5.	It helps in remineralisation and as a bone filler material.	It is used in the repair of bony defects of the jaw and bone loss arising from periodontal disease.	It would completely resorb and regenerate bone in the defect. It demonstrated excellent bonding to both bone and soft tissues.	-
5)	Activioss™ (NORAKER - France)	45% SiO_2, 24.5% Na_2O, 24.5% CaO and 6% P_2O_5.	The intrinsic properties of Activoss™helps to promote the natural process of bone regeneration.	It is used in dental implants.	Activioss™ has a higher degree of bioactivity and accelerates natural bone regeneration. It has the ability to inhibit bacterial proliferation.The mineral ion formula of Activioss™ increases its biocompatibility	It is present only in the form of granules and it has a complex manufacturing process.

					and removes the risk of transmitting pathogens.	
6)	Bioglass™ (US Biomaterials Corporation, Alachua, FL, USA)	45S5 - 45% SiO_2, 24.5% Na_2O, 24.5% CaO and 6% P_2O_5.	The bioactive hydrated silica layer that forms on the surface supports cell-matrix adhesion and facilitates tissue ingrowth and conduction.	Bioglass™ is commonly used for bone grafts[6].	High bioactivity is the main advantage of Bioglass™ . It is comparatively soft in comparison to other glasses. It can be machined, preferably with diamond tools, or ground to powder.	Mechanical weakness, low fracture resistance due to amorphous 2-dimensional glass network. The bending strength of most bioglass is in the range of 40-60 MPa which is not enough for load-bearing application.

Evidences:

S.No.	Author and Reference no.	Study and Control Group	Results
1)	Satyanarayana KV, et al[9].	24 localized aggressive periodontitis patients with bilaterally located three-walled intra-bony defect depth with 2 mm and pre-operative probing depths of 3mm were selected. 12 patients each were treated with and without BAG respectively.	Changes in gingival recession showed no significant differences. Highly significant improvements in the probing depth(PD), clinical attachment level (CAL) and bone defect depth were recorded after 12 months with regenerative material.
2)	Kumar PG, et al.[10]	20 defects in 10 patients were treated with open flap debridement and composite bone graft implantation(Hydroxyapatite, tricalcium phosphate, and bioactive glass) and another group of 10 patients were treated with open flap debridement alone.	A statistically significant ($P<0.05$) improvement in all parameters (namely PD, CAL, percentage defect fill, and linear bone growth) was observed in both groups of patients. However, the test group showed better clinical and radiographic outcomes when compared to the control group ($P<0.05$). The new composite alloplast resulted in better treatment outcomes than open flap debridement alone.
3)	Sculean A, et al.[11]	50 patients with one deep intra-bony defect were selected. 25 patients were randomly treated with a combination of enamel matrix protein derivative and a bioactive glass (EMD+BAG). The remaining 25 were treated with EMD alone.	Between the treatment groups, no statistically significant differences in the baseline and CAL were observed at 1 and 4 years. The results indicate that the clinical improvements obtained with both regenerative modalities can be maintained over a period of four years.
4)	Han J, Meng H, et al[12].	10 patients with 20 periodontal intra-bony defects were selected. 13 defects in five patients	Bleeding Index(BI), PD and CAL in BAG group was significantly lower

		were treated with OFD and BAG. 7 defects in 5 patients were treated with OFD alone.	than those in OFD group. The bioactive glass is effective as an adjunct to conventional surgery in the treatment of intra-bony defects.
5)	Subbiah R, Thomas B.[13]	8 systematically healthy volunteers each having 2 collateral sites with >6 mm clinical probing depth and radiographic evidence of an intra-bony defect were chosen. Randomly one defect was treated with OFD plus bioactive glass (PerioGlas®) and the other defect was treated with OFD alone.	The plaque index, gingival index, PD showed no statistical difference between any of the test and control sites at any point of time. However, radiographically, bioactive glass group showed significant improvement in bone fill over the sites with OFD alone. The alloplastic bone graft material, PerioGlas® demonstrated clinical advantages beyond that achieved by debridement alone.

Antibacterial properties:-

One of the most important properties of bioactive glasses is their ability to exhibit antibacterial activity, which creates a bacteria free environment while healing and regenerating the defect area. The antibacterial action of silica based melt-derived bioglass was investigated against certain types of microorganisms and the results were promising[14]. Stoor et al. in 1998[15] assessed the antibacterial efficacy of BAG paste on oral microorganisms such as Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis, Actinomyces naeslundii, Streptococcus mutans and Streptococcus sanguis. The authors determined that among all the periodontal microorganisms examined in the study, Streptococcus sanguis was the only microbe that had viable cells left even after 60 min following incubation in suspension of BAG (S53P4).The anti-microbial activity of BAG can be attributed to a pH-related phenomenon. Stoor et al.[15] reported that the BAG increased the pH to around 7.75 which was responsible for its anti-microbial activity. The alkaline nature of BAG not only contributes to antimicrobial activity, it might also be an important determining factor for periodontal regeneration. Han et al.[16] reported the change in pH induced by BAG, contributed to a reduction in inflammation at the periodontal defect site.Allan et al in 2001[17], studied the antibacterial effect of particulate bioactive glass on a range of oral bacteria. Streptococcus sanguis, Streptococcus mutans and Actinomyces viscosus were suspended in nutrient broth (NB), artificial saliva (AS) or Dulbecco's modified eagle medium plus 10% foetal calf serum (DMEM + 10%FCS), with or without particulate Bioglass. All bacteria showed reduced viability following exposure to Bioglass in all the media after 1 h. This antibacterial effect increased after 3 h. Porphyromonasgingivalis, Fusobacterium nucleatum, Prevotella intermedia and Aggregatibacter actinomycetemcomitans were suspended in either BM broth or 40% horse serum (HS) in RPMI. A considerable reduction in viability was observed with all bacteria tested, in both media, compared to inert glass controls. In further experiments it was found that the viability of S. sanguis was significantly reduced following exposure to NB pre-incubated with Bioglass. Additionally, it was found that neutralisation of this highly alkaline solution eliminated the antibacterial effect. Moreover, a solution of NB and NaOH (of equivalent pH) exerted an antibacterial effect of similar magnitude to that of the solution pre-incubated with Bioglass. Thus, particulate Bioglass exerts an antibacterial effect on certain oral bacteria, possibly by virtue of the alkaline nature of its surface reactions. This may reduce bacterial colonisation of its surface in vivo[17]. Tai et al. in 2006[18] performed a 6 weeks clinical study wherein the authors evaluated the antigingivitis and anti-plaque effects of a dentrifice containing BAG (Novamin) as compared with a placebo dentrifice. The authors observed a significant reduction in gingival bleeding and supravaginal plaque in the Novamin group as compared to the placebo. These observations allow us to conclude that BAG has an antimicrobial activity against early colonizers. This effect may be advantageous for a predictable regenerative periodontal therapy as bacterial recolonization can hamper the therapeutic success[19].

The reactions of bioglass in an aqueous environment, leading to osseointegration prompted scientists to check its antibacterial activity[17]. Bioactive glasses have antimicrobial activity in aqueous solutions due to the release of their ionic compounds over time[20]. The release of the dissolution products result in a high pH environment[21], capable of killing microbes[17,22,15]. In addition, the release of silica has been also linked to the antibacterial activity of bioactive glasses[23]. An in vitro study showed that S53P4 could kill pathogens connected with enamel caries (Streptococcus mutans), root caries (Actinomyces naeslundii, S. mutans) and periodontitis (Aggregatibacter actinomycetemcomitas)[24]. S53P4 and other compositions of bioactive glass with concentrations higher than 50mg/dl in the broth cultures of 16 different bacteria showed antibacterial properties due to an increase in pH[24]. The ideal bioactive glass material should include antibacterial elements to promote its antibacterial activity. This can prevent infections and reduce post-operative sensitivity[2]. The widely considered elements for this purpose are metals which have bioactivity against mico-organisms and can overcome the problems related with the low stability of other organic antimicrobial compounds during biomaterial processing[25]. Metals such as Ag, Cu, Zn have shown antibacterial properties[17] and are used as antibacterial elements in bioactive glasses.

Silver:-
Antimicrobial properties of silver have been known for centuries[26]. Three possible mechanism for bacterial growth inhibition by silver have been proposed: Interference with electron transport, binding to DNA, and interaction with the cell membrane. Silver ions can easily be introduced into a glass and then released during dissolution. The sol-gel derived composition of 76% SiO_2, 19% CaO, 2%P_2O_5 and 3%Ag_2O (by weight) is the first antibacterial glass which contains silver[27]. The low concentrations of the sol-gel glass that can be bactericidal are not toxic to human osteoblasts[28]. Silver-doped melt-derived glasses have also improved bactericidal properties compared to silver-free equivalent glasses[29].

Copper:-
Copper and its alloys, such as brass, bronze, copper-nickel and copper-nickel-zinc can be used in antimicrobial applications[30].Copper has the potential to disrupt cell function in several ways. Since several of these mechanisms may be acting simultaneously, this may reduce the ability of the microorganisms to develop resistance to copper[30].The strong antimicrobial ions of copper can be doped to different matrices such as polymers of ceramics[31,32]. Copper is not only an excellent antimicrobial agent but also has an essential role in bone formation and healing[33].

Zinc:-
Zinc is another metal which is thought to have antimicrobial properties and beneficial cellular response, but it can also cause toxicity[34]. Because of its anti-inflammatory and anti-micorbial properties, dentrifices with 2% zinc citrate have been used in the treatment of poor gingival health[35].

Bioactive and biocompatible coatings on implants with improved antibacterial properties can,
- ❖ Protect the metallic implant from corrosion by preventing the release of cytotoxic metallic ions[3].
- ❖ Deliver antimicrobial agents directly on the implant site[36].
- ❖ Promote new bone formation due to their bioactivity[31].

Discussion:-
The successful regeneration of periodontal structures primarily depends on the absence of infection. Significant contributing factors include an atraumatic surgical procedure, complete removal of infected periodontal tissue and thorough post-operative maintenance. However, despite best efforts there have been instances of infected periodontal grafts and membranes. Therefore, the incorporation of a bacteriostatic or bactericidal agent into a bone graft or membrane could prove beneficial.

With the advent of BAG, there have been evidences of the antibacterial dynamics of these grafts. Most investigators agree that the ionic makeup of BAG's primarily contribute to such an effect. With the dissolution of ions, there is an increase in pH which is responsible for an increase in alkalinity, thus probably neutralising the growth dynamics of periodontal bacteria.

The ionic dissolution of these glasses appear to be dependent on the ionic species and concentration present within the glass. Zhang et al.[24] positively correlated higher pH values with increased antimicrobial properties. An increase concentration of calcium ions also appeared to increase the antimicrobial effect of the glass. Another noteworthy finding was that the ionic concentration was highest within the first two hours of dissolution which would suggest maximum bacterial suppression.

Studies by Alan[17], Waltimo[22], Stoor,[23] have demonstrated antimicrobial effects against both primary and secondary colonizers in dental plaque. This may be an important factor in reducing bacterial contamination of grafts, thereby improving the chances of periodontal regeneration.

However, a major drawback appears to be the lack of evidence within animal models as the ionic concentration of blood may largely vary from in vitro solution. Future studies could incorporate this to demonstrate greater evidence of such an effect.

Conclusion:-

Bioactive glasses may soon become the future gold standard graft either on its own or as a composite graft in combination with other grafts and regenerative techniques. With more evidence of its unique property coming to light, BAG may soon have many specific ion species and concentrations to improve the prognosis of certain periodontal defects.

References:-

1. Savage, Amir, Eaton, et al. A systematic review of definitions of periodontitis and methods that have been used to identify this disease. Journal of Clinical Periodontology.2009;36(6):458-467.
2. Abbasi Z, Bahrololoom ME, Shariat MH, Bagheri R. Bioactive Glasses in Dentistry: A Review. J Dent Biomater. 2015;2(1):1-9.
3. Farooq I, Imran Z, Farooq U, Leghari A, Ali H. Bioactive Glass: A Material for the Future. World J Dent 2012;3(2):199-201.
4. De Carvalho M.F.F., Fernandes R.Z.D. et al. Bioactive glass with antimicrobial agents: In vitro evaluation. J. Med. Med. Sci. 2014;5(5):109-112.
5. Xiang, Y. And J. Du. Effect of Strontium Substitution on the Structure of 45S5 Bioglasses.Chemistry of Materials. 2011;23(11): 2703-2717.
6. Ahmed Salah Hameed, Ahmed Muhammed Abass, et al. Effect of Zinc on Antibacterial Action of Bioactive Glass Coating for Dental Implant. Medical Journal of Babylon. 2015; Vol.12. No.3: 612-617.
7. Jones JR, Gentleman E. Et al. Bioactive glass scaffolds for bone regeneration. Elements. 2007;3(6):393-99.
8. N. Li et al. Preparation and characterization of macroporous sol-gel bioglass. Ceramics International. 2005;31(5):641-646.
9. Satyanarayana KV, et al. Clinical evaluation of intrabony defects in localized aggressive periodontitis patient with and without bioglass - An in vivo study. Kathmandu Univ Med J. 2012 Jan-March; 10(37):11-15.
10. Kumar PG, et al. Volumetric analysis of intrabony defects in aggressive periodontitis patients following use of a novel composite alloplast - A pilot study. Qunitessence Int. 2011 May; 42(5):375-84.
11. Sculean A, et al. Four year results of a prospective controlled clinical study evaluating healing of intrabony defects following treatment with an enamel matrix protein derivative alone or combined with a bioactive glass. J Clin Periodontol. 2007 Jun; 34(6): 507-13.
12. Han J, et al. Clinical evaluation of bioactive glass in the treatment of peridontal intrabony defects. Zhonghua Kai Qiany Yi Xue Za Zw. 2002 May;37(3): 225-27.
13. Subbiah R. Thomas B, et al. Efficiency of a bioactive alloplast in the treatment of human periodontal osseous defects - A clinical study. Med Oral Pathol Cir Buccal 2011 March;16(2):339-44.
14. Brown, LS; Darmoc, MM; Havener, MB; Clineff, TD. Antibacterial effects of 45S5 bioactive glass against four clinically relevant bacterial species. 55th Annual meeting of the Orthopaedic Research Society.
15. Stoor P, Soderling E, et al. Antibacterial effects of a bioactive glass paste on oral microorganisms. Acta odontol Scand. 1998;56:161-65.
16. Han J, Meng H, Xu L, Chou L. Anti-inflammatory effect of bioactive glass on human periodontal intrabony defects. J Dent Res. 2002;81:A–129.
17. Allan I, Newman H, Wilson M. Antibacterial activity of particulate bioglass against supra and subgingival bacteria, Biomaterials. 2001;22:1683-87.
18. Tai BJ, Bian Z, Jiang H, Greenspan DC, Zhong J, Clark AE, et al. Anti-gingivitis effect of a dentifrice containing bioactive glass (novamin) particulate. J Clin Periodontol. 2006;33:86–91.
19. Ram Sabarish Chandrasekar et al. Evaluation of antimicrobial properties of bioactive glass used in regenerative periodontal therapy. J Indian Soc Periodontol. 2015 Sep-Oct; 19(5): 516–519.
20. Zehnder M, et al. Dentin enhances the effectiveness of bioactive glass S53P4 against a strain of Enterococcus faecalis. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology 2001, 101:530-35.
21. Sepulveda P, Jones JR, Hench LL. In vitro dissolution of melt-derived 45S5 and sol-gel derived 58S bioactive glasses. Journal of Biomedical Materials Research 2002, 61:301-11.
22. Waltimo T, Brunner TJ et al. Antimicrobial effect of nanometric bioactive glass 45S5. J Dent Res.2007;86:754-757.

23. Zehnder M, Luder HU, Schätzle M, Kerosuo E, Waltimo T: A comparative study on the disinfection potentials of bioactive glass S53P4 and calcium hydroxide in contralateral human premolars ex vivo. International Endodontic Journal 2006, 39:952-958.
24. Zhang D, Lepparanta O, et al. Antibacterial effects and dissolution behaviour of six bioactive glasses. J Biomed Mater Res. 2010;92:475-83.
25. Plaza H, Escobar B, et al. Designing antimicrobial bioactive glass materials with embedded metal ions syntheisized by the sol-gel method. J Mater Sci Eng C. 2013;33:3795-3801.
26. Vidya Krishnan and T. Lakshmi. Bioglass: A novel biocompatible innovation. J Adv Pharm Technol Res. 2013;4(2): 78–83.
27. Bellatone M, Coleman NJ, Hench LL. “Bacteriostatic action of a novel four component bioactive glass”. J Bio med Matr Res. 2000;51:484-490.
28. El-Kady AM, Ali AF, Rizk RA, et al. “Synthesis, characterization and microbiological response of silver doped bioactive glass nanoparticles.” Ceram Int. 2012;38:177-188.
29. Blaker J.J., et al. Development and characterisation of silver-doped bioactive glass coated sutures for tissue engineering and wound healing applications. Biomaterials 2004; 25(7-8):1319-1329.
30. Michels H, et al. Copper alloys for human infectious disease control. Stainless steel. 2005, 77000;20:20.
31. Abou Neel EA, Ahmed I, Pratten J, et al. Characterization of antibacterial copper releasing degradable phosphate glass fibres. Biomaterials. 2005;26:2247-2254.
32. Gérard C, T.Brunner Waltimo TJ, Vollenweider M, et al. Antimicrobial effect of nanometric bioactive glass 45S5. J Dent Res. 2007;86:754-757.
33. Bordeleau LJ, Barralet J, et al. The stimulation of angiogenesis and collagen deposition by copper. Biomaterials. 2010;31:824-831.
34. Aina V. Et al. Cytotoxicity of zinc containing bioactive glasses in contact with human osteoblasts. Chem Biol Interact. 2001; 167:207-18.
35. Saino E, Grandi S, Quartarone E, et al. In vitro calcified matrix deposition by human osteoblasts onto a zinc containing bioactive glass. Eur Cells Mater. 2011;21:59.
36. Nandi, et al. In vitro and in vivo release of cefuroxime axetil for bioactive glass as an implantable delivery system in experimental osteomyelitis. Ceram Int., 2009; 35(8):3207-3216.