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Clinical applications of Bioactive glass S53P4 in bone infections: a systematic review

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Abstract. – OBJECTIVE: Treatment of osteomyelitis, in of itself, is challenging but is further complicated by attendant bone infections. The management of bone infection, and bone rebuilding may be assisted by the use of bioactive glasses (BAGs) which have antimicrobial and osteo-stimulative proprieties. However, this clinical application and potential complications associated with BAGs (e.g., BAG S53P4), are poorly defined. The aim of this study is to review the results of clinical research using BAG S53P4 in the treatment of human bone infections.

MATERIALS AND METHODS: This review was conducted in accordance with the PRISMA statement. The following databases were searched: PubMed, Cochrane Library, EMBASE, and Scopus. We examined electronic databases from 1965 to 2018 using different combinations of the following keywords: "S53P4", "BonAlive", "infection" and "osteomyelitis".

RESULTS: Eight studies were considered which included a total of 276 cases (mean age of 49.3 years). The most frequent pathogen isolated was *Staphylococcus aureus*. A one-step surgical procedure was performed in 89.85% of cases. Good clinical and radiological outcomes were reported with a mean follow-up of 21.5 months. Twenty-three complications (8.3% of total cases) were described with the recurrence of bone infection as the most common complication (6.15% of total cases).

CONCLUSIONS: BAG-S53P4 seems to be useful bone filler in orthopaedic surgery for osteomyelitis treatment. The attendant clinical results and associated rate of complications associated with BAG S53P4 use are comparable with those of other techniques in the short term. However, long-term follow-up studies are required in order to confirm the longevity of this treatment.

Key Words
S53P4, Bioactive glass, Osteomyelitis, Bone infection.

Introduction

Osteomyelitis remains one of the most challenging disorders complicating orthopaedic surgery[1,2]. Bacterial infection is the predominant cause of this condition which is manifested in the inflammatory destruction of bone[3]. The most common pathogen to mediate osteomyelitis is *Staphylococcus aureus;* other less frequently associated pathogens include other Gram-positive and negative bacteria such as *S. epidermidis* and *Pseudomonas spp*, while fungal infections are rare and are more typical of immunosuppressed patients[4,5].

Infections most frequently arise from haematogenous colonisation (often in children), or post-traumatic (open fractures) and post-operative direct inoculation[3,6,7].

Patient predisposing factors include diabetes, peripheral vascular disorders, smoking, and alcoholism all of which may also contribute to an unfavorable outcome[8].

Clinical features of acute osteomyelitis include local swelling, fever, pain and infected secretions (9,10). Failed antimicrobial treatment may lead to a chronic phase characterized by bone necrosis and chronic fistulae[11].

Antibiotic therapy alone often fails to eradicate the infection[9] because of its limited ability to penetrate poorly vascularized or devitalized bone[1]; consequently, bone and soft tissue debridement combined with antibiotics are indicated[12].

Various techniques are available for the restoration of bone defects including: (i) free vascularized bone grafts, (ii) granulation formation according to the Masquelet technique[13], (iii) bone transport based on the Ilizarov technique[12], (iv) antibiotic-loaded polymethylmethacrylate (PMMA) cement[14] and (v) bone substitutes.

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The most common therapeutic treatment of chronic osteomyelitis is a two-stage procedure beginning with aggressive surgical debridement and defect filling with gentamicin-loaded PMMA beads, then followed by reconstruction of the bony defect[5].

This treatment paradigm is accompanied by significant risks including: (i) possible thermal damage to antibiotics and to bone cells adjacent to the cement, (ii) potential antimicrobial resistance with associated biofilm formation due to insufficient antibiotic concentration and (iii) the need for follow-up surgery to remove PMMA beads[7]. Many patients undergo numerous surgical procedures resulting in protracted hospital stays with an increased risk of comorbidity[10,15].

Recently, new biomaterials have been proposed to overcome some of these problems[16], and include antibiotic-loaded hydroxyapatite (HA), calcium-phosphate (CP), and calcium-sulphate (CS)[17-19]. These preparations (i) fill the dead space, (ii) don't require harvesting and processing, (iii) have unlimited availability, (iv) do not require subsequent surgical removal, and (v) have a predictable antibiotic release.

Nonetheless, antibiotic resistance has been observed with these materials. In response to these limitations, bioactive glasses (BAGs) have been introduced.

The most widely used BAG is bioactive glass-S53P4 (BAG-S53P4) with the specific composition (by weight) of 53% SiO_2, 2.4% P_2O_5, 23% Na_2O, and 20% CaO. The antibacterial effect of BAG-S53P4 is based on the local release of phosphorus salts, as well as sodium and calcium ions[20] which collectively increase local pH and osmotic pressure and thereby inhibit bacterial adhesion and proliferation. This mechanism is not associated with the development of antibiotic resistance and prevents the formation of bacterial biofilms *in vitro*[21-23].

This deposition of ions also forms a silica gel layer near the glass surface to which amorphous calcium phosphate precipitates and subsequently crystallizes into natural hydroxyapatite. The osteo-stimulative properties of this layer activate osteogenic cells and potentially promotes angiogenesis[24].

BAG-S53P4 may be used directly in the infected site through a one-stage surgical procedure which results in a less invasive and more cost-effective treatment for patients and the health-care system overall.

The aim of our study was to systematically review the results of all clinical studies using BAG-S53P4 in the treatment of human bone infections. As BAG-S53P4 is being more widely and frequently used, there is a pressing need to assess its effectiveness and safety on the basis of clinical outcomes and radiological evidence.

Materials and Methods

Focused Question Based

Based on the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines, a specific question was constructed. The focused question was ''What are the clinical outcomes of BAG-S53P4 in the treatment of osteomyelitis?".

Eligibility Criteria

The following eligibility criteria were required: (i) original clinical studies; (ii) patients with orthopaedic osteomyelitis treated with BAG-S53P4 (BonAlive, BonAlive Biomaterials Ltd, Biolinja, Finland); (iii) inclusion of case-control and cohort study; and (iv) intervention: patients treated with one or two stage surgery. Letters to the editor, historical reviews, case reports, unpublished articles, studies that consider ENT and cranial osteomyelitis, were excluded.

Search Strategy and Study Selection

PubMed/Medline (National Library of Medicine, Washington, DC), EMBASE and Scopus databases were searched from 1965 up to and including 2018 using the following combination of keywords; (i) "S53P4" AND "infection"; (ii) "S53P4" AND "osteomyelitis"; (iii) "BonAlive" AND "osteomyelitis" and (iv) "BonAlive" AND "infection".

We also searched the databases using the following combinations of MeSH terms: (i) "bioactive glass S53P4" AND "Osteomyelitis"; and (ii) "bioactive glass S53P4" AND "Infection".

Titles and abstracts of studies identified using the above-described protocol were screened by two authors (NZ and AL) and checked for agreement. Full-texts of studies judged by title and abstract to be relevant were read and independently evaluated for the stated eligibility criteria. Reference lists of potentially relevant original articles were hand-searched to identify any studies that could have remained unidentified in the previous step. A search using "similar article" was done for the papers selected. Once again, the articles were checked for agreement via discussion among the authors.

Results

Study Selection

The search results are shown in Figure 1, according to PRISMA guidelines[25]. The initial search yielded 170 studies. One hundred and sixty-two, which did not fulfill the eligibility criteria, were excluded (Figure 1). In total, eight studies[1,5,9-11,20,26,27] were included and processed for data extraction. Study names were assigned comprising first author and year of first publication (Table I). Year of publication ranged from 2010 to 2017.

Study Characteristics

Study characteristics are summarized in Tables I and II. We included three retrospective cohort studies[10,11,26], one prospective multinational multicenter cohort study[5], two retrospective case-control studies[1,20] and two case series[9,27].

Methodological Study Quality Assessment

The Newcastle-Ottawa Scale[28] (NOS) was used to grade the methodological quality of each study assessed in this review (Table III).

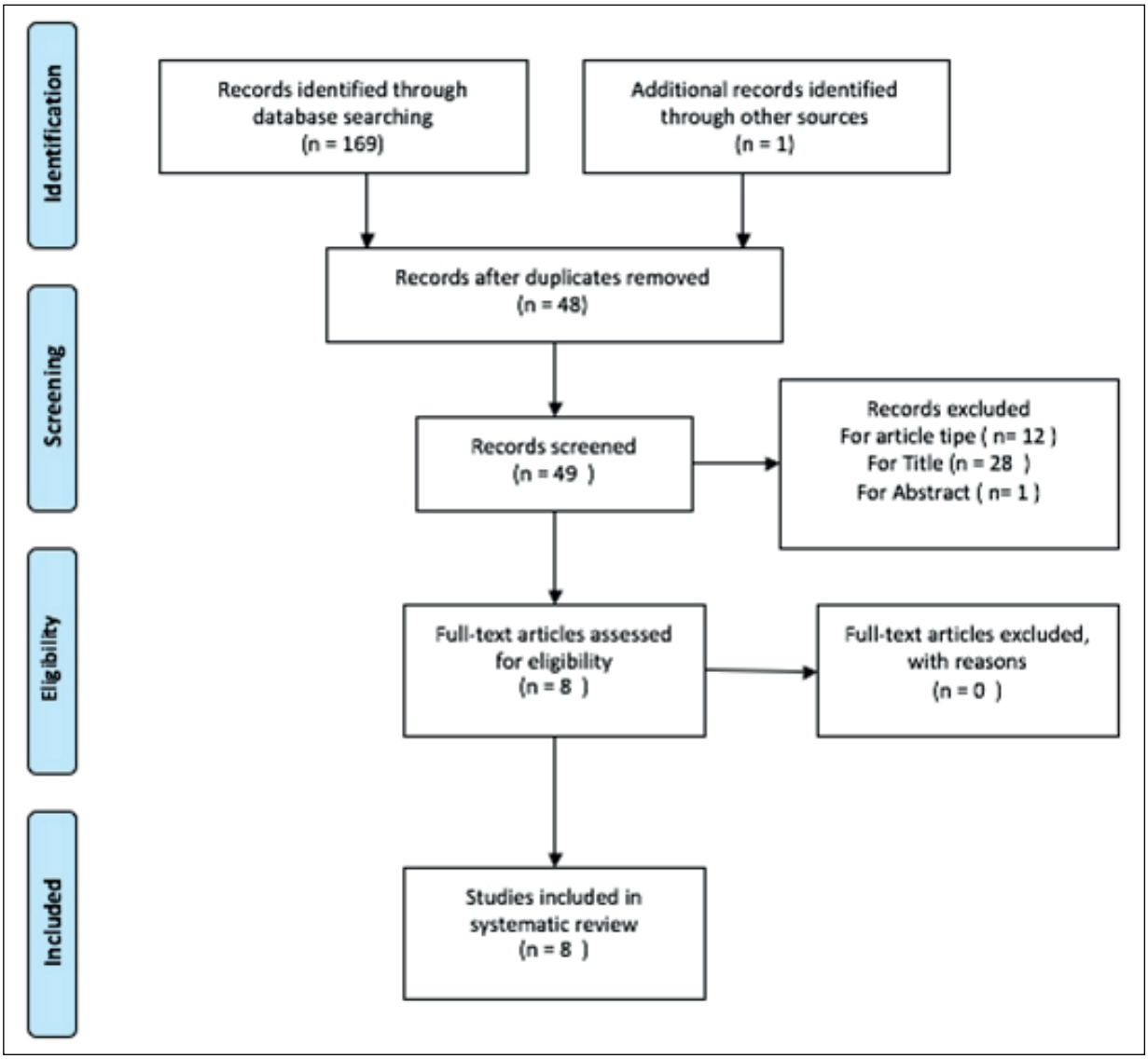

Figure 1. PRISMA flow diagram.

Table I. Summary of reviewed studies with bioactive glass-S53P4 used in orthopedic surgery for bone infections.

Authors	Study Groups	Application form of S53P4/ associated local device	Site of infection	Outcomes of study
Lindfors et al (2010)[11]	Group 1: S53P4[11]	S53P4 Granules. In one patient metal implant covered with BAG was used.	Lower limb[10] Spine[1]	Complete healing for 9 patients. Complications in 2 patients: - Soft tissue infection due to necrosis of local flap. No sign of bone infection. - Deep infection due to haematoma (insufficient
McAndrew et al (2013)[9]	Group 1: S53P4[3]	S53P4 Granules. No other local devices.	Group 1: Tibia[1], Femur[1], Ulna[1]	Excellent results in all three patients
Drago et al (2013)[26]	Group 1: S53P4[27]	S53P4 Granules. No other local devices.	Tibia[18] Femur[7] Foot[1] Humerus[1]	Good results in 24 patients. Infection recurrence in 3 patients: - Bone infection due to insufficient filling of the cavity (involvement of all medullary space previously occupated by the nail and not only the primary cavity). - Soft tissue infection due to suffering skin closure resolved with fasciocutaneous flap in one case and additional stiches in the other.
Romanò et al (2014)[20]	Group 1: S53P4 (n=27) Group 2: antibiotic-loaded hydroxyapatite and calcium sulphate (n=27) Group 3: tricalcium phosphate + antibiotic-loaded demineralized bone matrix (n=22)	S53P4 Granules No other local devices.	Group 1: 18 Tibia, 8 Femur, 1 Humerus, 1 Other. Group 2: 15 Tibia, 10 Femur, 1 Humerus, 1 Other. Group 3: 14 Tibia, 7 Femur, 1 Humerus.	Same clinical results in terms of recurrence of infection compared to other groups. reduction in prolonged wound serum leakage and a trend in reduction of hospital stay with S53P4.

Continued

Table I (Continued). Summary of reviewed studies with bioactive glass-S53P4 used in orthopedic surgery for bone infections.

Authors	Study Groups	Application form of S53P4/ associated local device	Site of infection	Outcomes of study
Lindfors et al (2016)[5]	Group 1: One step with S53P4[98] First step with antibiotic beads (Septopal®) second step with S53P4[18]	S53P4 Granules. No other local devices.	Group 1: Tibia[62], Femur[28], Calcaneus[13], Fibula[7], Ulna[1], Metatarsal[3], Olecranon[2], Humerus[1], Cuneiform[1], Methacarpus[1], Phalang[1]	S53P4 90% of success rate. Poorer Outcome after two stages procedure (BIAS= was just after the European approval of the glass, used only after failure of antibiotic beads). Strong correlation between systemic host grade and complication after infection treatment
Kankare et al (2016)[27]	Group 1: S53P4[3]	Patients 1 & 2: S53P4 Granules covering vertebral body expander Patient 3: S53P4 Granules+bone autograft covering vertebral body expander.	Group 1: Spine[3]	Complete healing in all three patients with bone fusion and neurological recovery.
Geurts et al (2016)[10]	Group 1: S53P4[15]	S53P4 Granules. No other local devices.	Group 1: Tibia[7], Femur[6], Calcaneus[1], Iliac Crest[1]	Infection healing in all fifteen patients with normalization blood tests and clinical appereance Refracture in 1 patient due to non-compliance to weight bearing indication. Treated with external fixator and completely healed.
Ferrando et al (2017)[1]	Group 1: S53P4[12] Group 2: calcium sulphate antibiotic beads[13]	S53P4 Granules. No other local devices.	Group 1: Tibia[7], Femur[4], Calcaneus[1]. Group 2: Tibia[6], Calcaneus[4], Femur[2].	Same clinical results in terms of recurrence of infection and complications.

Table II. Study characteristics. F, female; M, male; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Authors	Number of Patients	Mean age/SD or range in years	Gender (F/M)	Systemic antibiotics use	Examination during follow-up	Months of follow-up
Lindfors et al (2010)[11]	11	Group 1: 51.45 (SD 20.55)	Group 1: 2/9	Yes, variable duration and type of antibiotics, cultures based.	Clinical and radiological evaluations (X-rays).	15
Drago et al (2013)[26]	27	Group 1: 44 (SD 14)	Group 1: 9/18	Yes, from 4 to 6 weeks after surgery cultures based	Blood testes: White cell count, CRP, ESR. Clinical and radiological evaluation (X-rays).	24
McAndrew et al (2013)[8]	3	Group 1: 44.5 (range 28-68)	Group 1: 1/2	Yes, variable duration and type of antibiotics, cultures based.	Blood testes: White cell count, CRP, ESR. Clinical and radiological evaluation (X-rays).	17
Romanò et al (2014)[20]	76	Group 1: 45.2 (SD 13.6). Group 2: 47 (SD 13.1). Group 3: 44.9 (SD 14.2).	Group 1: 8/19. Group 2: 11/16. Group 3: 8/14.	Yes, 12 weeks cultures based.	Blood testes: White cell count, CRP, ESR. Clinical evaluation.	36
Lindfors et al (2016)[5]	116	Group 1: 48 (range 15-87)	Group 1: 32/84	Yes, variable duration and type of antibiotics, cultures based.	Clinical and radiological evaluation (X-rays).	12 minimum
Kankare et al (2016)[27]	3	Group 1: 68.33 (range 53-80).	Group 1: 1/2	Yes, variable duration and type of antibiotics, cultures based.	Blood testes: White cell count, CRP, ESR. Clinical and radiological evaluation (X-rays and CT).	From 8 to 48
Geurts et al (2016)[10]	15	Group 1: 51 (range 14-57)	Group 1: 4/11	Yes, variable duration and type of antibiotics, cultures based.	Blood testes: White cell count, CRP, ESR. Clinical and radiological evaluation (X-rays).	21,6 (From 5,4 to 47,4)
Ferrando et al (2017)[1]	25	Group 1: 50 (SD 18) Group 2: 48 (SD 17)	Group 1: 1/11 Group 2: 4/9	Yes, variable duration and type of antibiotics, cultures based.	Blood testes: White cell count, CRP, ESR. Clinical and radiological evaluation (X-rays).	22

Table III. Newcastle Ottawa Scale.

Study	Selection				Comparability		Exposure			Number of star
	S1	S2	S3	S4	C1	C2	E1	E2	E3	
Lindfors et al (2010)[11]	X		X		X	X	X	X	X	7
Drago et al (2013)[26]	X		X		X	X	X	X	X	7
McAndrew et al (2013)[9]	X	X			X		X	X		5
Romanò et al (2014)[20]	X	X			X	X	X	X	X	7
Lindfors et al (2016)[5]	X	X	X		X	X	X	X	X	8
Kankare et al (2016)[27]	X	X		X		X	X			5
Geurts et al (2016)[10]	X	X			X	X	X	X	X	7
Ferrando et al (2017)[1]	X	X			X	X	X	X	X	7

In summary, the NOS scale uses a systematic approach based on 3 specific criteria: Selection (S), Comparability (C) and Exposure (E), which are subdivided in 9 criteria: (S1) adequate case definition; (S2) representativeness of the cases; (S3) selection of control; (S4) definition of control; (C1) comparability of cases; (C2) controls on the basis of the analysis; (E1) ascertainment of exposure; (E2) same method of ascertainment for cases and controls; (E3) non-response rate. Each criterion was given a response of either ‘‘Yes”, ‘‘No”, or ‘‘cannot tell,”. Each study could have a maximum score of 9.

Patients Characteristics

Two hundred seventy-six patients (81 female; 195 male) were included with a mean age was 49.3 years[14-87]. All patients had a clinically- and radiologically-diagnosed osteomyelitis. Two hundred forty-eight patients (89.85%) received a one-step procedure and 28 patients (10.15%) received two or more surgeries[5,11,26].

Bone Infection Site

The tibia, femur and calcaneus bones most frequently required clinical remediation: (i) tibia (n=132), (ii) femur (n=73), and (iii) calcaneus (n=19), accompanied by assorted other sites (n=52) (Table 1). The most frequently reported pathogen, among others, was *S aureus* (Figure 2). Mixed flora were found in 42 patients, but with inconsistent reporting of exact poly-microbial infections; consequently, a “Mixed Flora” section is not included in the “Bacterial” section. There was only a single report of a fungal infection.

Outcomes Reported

The mean time to follow-up examinations was 21.5 (5.4 to 47.4) months. Blood tests and outcomes evaluated at the last follow-up are reported in Table II. Good to excellent clinical results were reported using bioactive glass in all studies (Table II). Lindfors et al[11] reported a success rate of 90.9% (10/11) in controlling bone infection with a mean follow-up of 24 months. Romanò et al[20] found comparable infection control rates in all groups (21 months follow-up); in particular, 92.6% in BAG-S53P4 group, 88.9% in antibiotic-loaded hydroxyapatite and calcium sulphate group, and 86.3% in a mixture of tricalcium phosphate and an antibiotic-loaded demineralised bone matrix group. Statistically significant reductions in wound serum leakage and reductions in hospital stays were reported in BAG-S53P4 groups compared with the other two antibiotic-loaded bone substitutes.

Drago et al[26] reported a success rate of 87.5% (21/24) with a mean follow-up of 18 months. Three patients were considered failed but only one reported recurrence in bone infection. Ferrando *et al*[1] reported comparable successful clinical outcome rates in a BAG-S53P4 group at 91.7% and in a calcium sulphate antibiotic beads group at 92.3% at 22 months follow-up. Lindfors

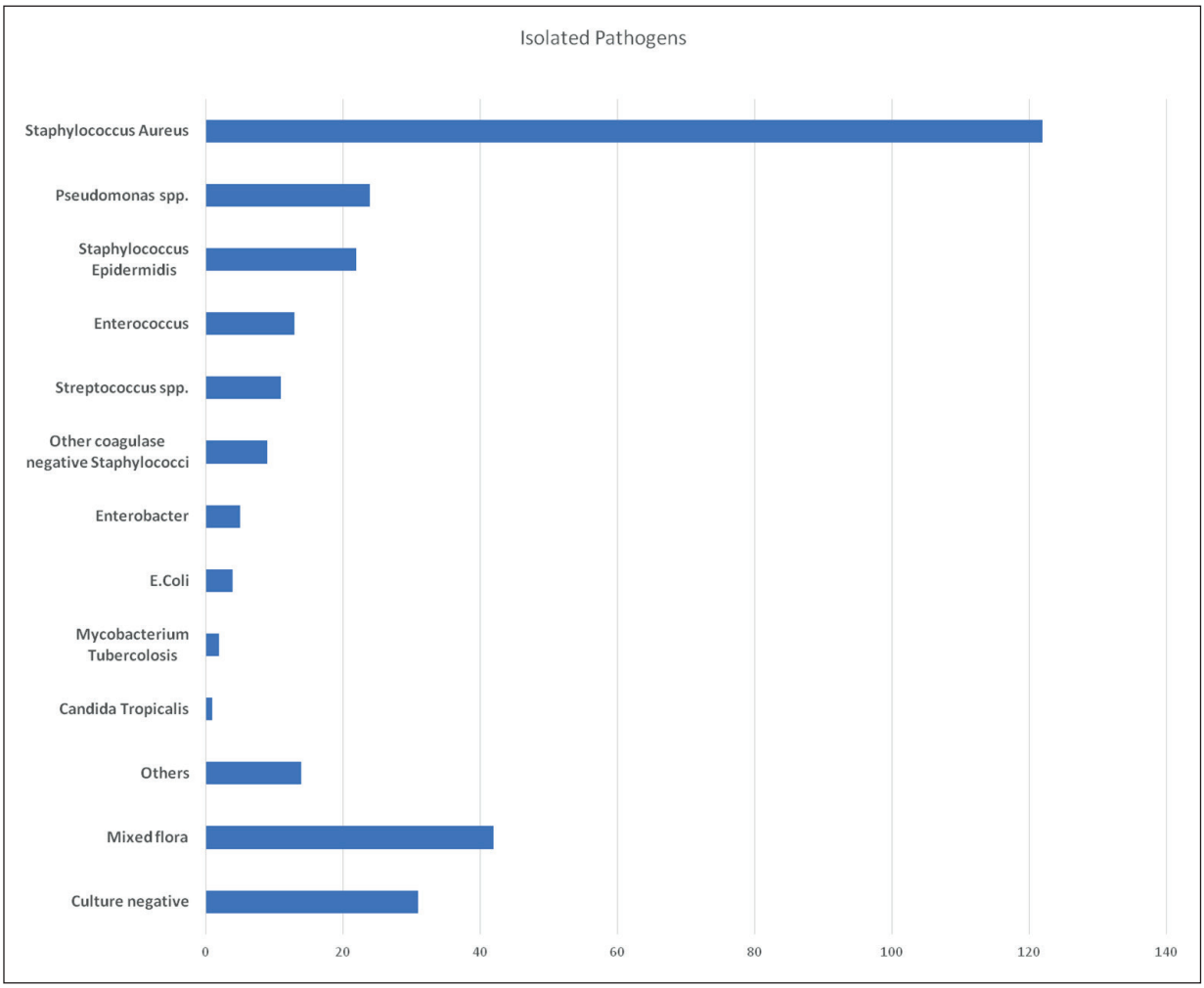

Figure 2. Isolated pathogens reported in bone infections treated with Bioactive glass S53P4. "Others" section include isolation of low incidence bacteria like: *Acinetobacter spp.* 3, *Corynebacterium spp.* 2, *Propinobacterium Acnes* 1, *Serratia spp.* 1, *Clostridium difficile* 1, *Citrobacter freundi* 1, *Streptococcus magnus* 1, Very resistant gram-negative bacilli 1, *Proteus mirabilis* 1.

et al[5] in their multinational, multi-center study reported excellent results with a success rate of 90% for their S53P4 group. Furthermore, they found a correlation between the incidence of multiple bacterial flora infections with the incidence of re-infection (21% re-infection in multiple flora infections). The worst treatment outcomes were observed as a consequence of two-stage surgeries and soft tissue defects requiring a local flap. Statistical analyses showed no correlation between persistence of infection (or re-infection) and age, gender, location, or Cierny or McPherson classification.

McAndrew et al[9] and Kankare et al[27] reported excellent result in all patients treated with bioglass. Kankare et al also described the efficacy of bioglass in fungal and mycobacterial vertebral infections.

Geurts et al[10] reported excellent clinical and instrumental results in all fifteen patient treated with BAG-S53P4.

Complications Reported

Postoperative complications were reported in 23 patients (8.3% of total cases) (1,5,7,9,11,26,27).

Bone infection recurrence was described in 17 patients (6.15% of total cases). Drago et al[26] reported tibia endomedullary nail infection where only the primary osteomyelitis cavity was filled with BAG-S53P4 and not all the medullary canal.

Lindfors et al[5] reported only one patient experienced a recurrence of deep infection due to a hematoma probably caused by insufficient filling of the cavity with BAG-S53P4. The biggest series of bone infection recurrence (12 patients) was reported by Lindfors et al[5].

Soft tissue infections were observed in four patients[1,11,26]. In one patient, necrosis of the free flap used to cover the skin defect without bone infection was observed[11]. Drago et al[26] reported two skin complication treated with a cutaneous skin flap in one case and with additional stitches in the other. Also, Ferrando et al[1] reported a delayed wound healing.

Others complications reported were a re-fracture due to non-compliance to weight bearing but was not accompanied by deep infection recurrence nor a seroma formation[1,10].

Discussion

Currently, the most widely used treatment for osteomyelitis is a two-stage procedure that involves an aggressive debridement in combination with the use of antibiotic containing PMMA beads in the first procedural stage. This method is open to criticisms including: (i) the time of antibiotic release is not always known, (ii) a prolonged antibiotic release can promote bacterial resistance, and (iii) it is possible that the beads may provide a receptive surface for pathogens producing biofilm[5]. In a long-term follow-up study of 100 patients treated with gentamicin-PMMA beads, relapses were observed for 8.8% of patients with acute osteomyelitis and for 21.2% of patients with chronic osteomyelitis[29].

More recently, the use of bioactive glass combined with systemic antibiotic therapy has demonstrated significant potential in the treatment of osteomyelitis[9]. A major benefit of using BAGs is the potential to use it in a one-stage treatment, avoiding additional surgery, and consequently reducing the risk for additional complications and thereby reducing the burden on health care systems[5]. Moreover, no adverse effects of bioactive glass have ever been observed.

BAG-S53P4 is especially effective in bone cavity management following debridement. Equally importantly, BAG-S53P4 is also an osteo-conductive biomaterial with bone-bonding, angiogenic and potent antimicrobial properties. A consequence of its intrinsic antimicrobial properties is that it is the only biomaterial approved in Europe for local application for the treatment of bone infections without being pre-loaded with antibiotics or acting as an antibiotic carrier[26].

BAG-S53P4 has the most effective bactericidal effects of all the tested BAGs with the fastest pathogen killing and growth inhibitory effects. BAG-S53P4 has been proven effective against aerobic- and anaerobic-pathogens multi-drug resistant bacteri[30].

The therapeutic effects of BAG-S53P4 on bone-regeneration appear to be associated with the glass surface. Activation of osteogenesis appears to begin with the exchange of Na^+ from the glass with H^+ and H_3O^+ from the surrounding tissues associated with the release of SiOH at the glass surface. After re-polymerization, a SiO_2-rich layer is formed. Due to the migration of Ca^{2+} and PO_4^{3-} groups to the surface and crystallization, a CaO-P_2O_5 hydroxyapatite layer is formed on top of the Si-rich layer. Osteoblast interactions with the hydroxyapatite layer on the glass activate bone formation[31].

The antibacterial properties of BAG-S53P4 have been tested *in vitro* for aerobic and anaerobic planktonic bacteria, as well as bacteria forming biofilm. The antibacterial properties arise from a dissolution reaction at the glass surface, leading to the elevation of the local pH and an increase of the local osmotic pressure which, collectively, makes the environment hostile for bacterial adhesion and proliferation[30,32]. This mechanism of action prevents the induction of resistance in the long term. Because of the continuous reactions and ongoing layer formation, the glass will eventually be absorbed[33,34].

BAG-S53P4 is known, as well, to stimulate the release of angiogenic growth factors thereby promoting angiogenesis. Evidence for stimulated angiogenesis arises from enhanced MRI and SPECT imaging which indicate ingrowth of fibrovascular tissue into the spaces between the glass granules[35]. Full vascularization of the bone substitute observed at a second operation provided evidence for promotion of local angiogenesis[31]. Furthermore, *in vitro* studies revealed enhanced endothelial cell proliferation and up-regulation of VEGF production as further support for BAG induced angiogenesis[36,37]. Other studies suggest the importance of altered cytokine profiles in tendon and bone healing; however, there is, as yet, insufficient evidence to present a meaningful hypothesis[38-41].

BAG-S53P4 is employed in various preparations, but is most commonly used in a granular form which better adapts to the shape of the cavity to be filled. It is proven that S53P4 granules enhance new bone formation to a larger extent than bioactive glass plates, probably due to the intergranular porosity and the much greater available surface area[42].

The antibacterial effect appears inversely related to granule size; large granules which present a smaller surface area per unit mass lead to a decrease in pH[43].

Nonetheless, there is a single report in which bone formation in a rabbit model was significantly greater when larger granules were used[44]. As yet, there is no report comparing the effectiveness of granule size in human bone healing. Nonetheless, it is critical to thoroughly fill the bone cavity in order to maximize effective treatment using BAGs.

As a consequence of its collective properties, treatment with BAG-S53P4 consistently results in a 90% or better success rate for treatment of osteomyelitis[45]. This success rate is independent of anatomical region, or the microorganism(s) involved. As a consequence, there has already been a change in one institutional protocol for the treatment of chronic osteomyelitis[10].

Unfortunately, the employment of BAGs does not mitigate lapses in surgical techniques. For example, inadequate surgical debridement overlooking minute osteomyelitic foci separated from the principle one still may result in re-infection. As well, wound complications like seroma formation may occur still[1].

Biomaterials (e.g., calcium sulfate-based bone substitutes) are associated with persistent postoperative serum wound leakage[46]. To illustrate, Romanò et al demonstrated that BAG-S53P4 treated patients showed significantly lower prolonged wound serum leakage (3.7%) compared to the two antibiotic-loaded calcium-based bone substitutes (29.6% and 27.2%); they also showed a trend towards reduction in hospital stay[7]. In the same way, seroma leakage was recorded for only three patients (2.6%) in the study of Lindfors et al[5]. Finally, the research of Ferrando et al[1] showed that two patients with seroma formation had a recurrence of infection at last follow-up.

Recurrence of infection has been reported in 17 cases; however, it is unknown if the second infection is *de novo* or simply a resurgence of the original infection. Future studies need to more carefully document the microbiology of these secondary infections in order to better understand the efficacy of BAGs and the causes of reinfection. Proper filling of the neo-cavity and adequate skin coverage without tissue tension are essentials in preventing osteomyelitis recurrence. Improperly filled bone cavity, which resulted in haematoma formation, was considered a source of infection recurrence in one patient reported by Lindfors et al[11]. Romanò et al[7] also showed that incomplete filling of a large bone cavity, resulting from removal of an infected nail in a knee-arthrodesis, resulted in an infection.

The use of skin flaps remains problematic. Lindfors et al[5] showed that the use of flaps was statistically associated with poorer outcomes compared to those cases in which flaps were not used. Flaps are more often used in severe cases involving large soft tissue damage. Drago et al (26) similarly presented two cases of treatment failure in patients with major soft-tissue defects in which flap coverage was employed at the time of debridement. In these two cases, the cover was finally achieved with direct closure accompanied by the high tension of the wound margins which resulted in wound healing problems. These findings underscore the importance of effective vascularity in the treatment of osteomyelitis.

Conclusions

The bioactive glass S53P4, with its angiogenic, osteo-stimulative and antibacterial properties, is a suitable bone void filler in the treatment of chronic osteomyelitis. Its effectiveness is independent of (i) etiology, (ii) pathogen species, (iii) localization, or (iv) previous treatment of the infection. Its one-stage surgical application and suitability in immunocompromised hosts (without the need for supplementary local antibiotics) make this treatment protocol biologically effective, patient-friendly, and cost-effective while reducing hospitalization duration and related complications. A proper filling of the defect and adequate soft tissue coverage are necessary to obtain satisfactory results.

Good to excellent results were reported in one stage and two stage procedures using BAG-S53P4. Multiple retrospective studies report outcomes in chronic osteomyelitis of the long bones treated with BAG-S53P4 comparable with antibiotic-loaded calcium-based bone substitutes[1,7]. However, rigorously controlled clinical studies are still lacking. Randomized, multicenter clinical trials need to be performed in order to determine if bioactive glass could be a suitable replacement of the current gold standard in the treatment of osteomyelitis.

Lastly, further studies focused on the employment of S53P4 for the treatment of pediatric bone infections and comparative studies analyzing the results obtained by using different shapes of

BAGs and different sizes of granules should be performed. An important consideration remains that paediatric patients have different anatomical and pathological characteristics compared to adults[47].

More prolonged follow-up periods are also necessary in light of the possibility of recurrence of chronic osteomyelitis, sometimes many years after treatment.

Conflict of Interests

The Authors declare that they have no conflict of interests.

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