Utilisation of bioactive glass S53P4 inside an induced membrane for severe bone defect with high risk of infection

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Utilisation of bioactive glass S53P4 inside an induced membrane for severe bone defect with high risk of infection: a multi-center preliminary experience

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ABSTRACT

Background: The induced membrane technique has been developed to address bone defect of critical size from various origins. Despite its exceptional efficacy, several cases underwent a failure, which is regularly associated with a septic problem. The best way to conduct in this situation remains debated.
Purpose: To estimate use of bioactive glass S53P4 (BAG-53P4) in induced membrane technique failures or with an anticipated high risk of failure.
Material and method: We conducted a retrospective analysis of patients from several medical centers in Europe where BAG-S53P4 has been used inside an induced membrane. The etiology of the defect, the bone fixation used, the delay the bioactive glass was placed, the reason why the bioactive glass was used and the results were reported.
Results: Eight cases were included (3 women and 5 men). Mean age was 43 years (16-82; Standard deviation 23). Mean height was 171 cm (162-184; SD 7), mean weight was 69 kg (60-85; SD 8) and Body Mass Index was 23,39 M/Kg2 (21,9-25,1; SD 1,22). Mean length of defect was 68 mm (40-100mm, SD 23). All patients received BAG-S53P4 granules (BonAlive Biomaterials Ltd, Turku, Finland) to fill the resultant cavity (3 as a stand-alone in the induced membrane and 5 mixed with autograft). Three patients were implanted with BAG-S53P4 during the second stage of a first induced membrane technique because of a high risk of infection (three open fractures); two patients were implanted with BAG-S53P4 during the second stage of a first induced membrane technique because of the great size of the defect (two infectious non-union); two patients were implanted with BAG-S53P4 as a third stage of induced membrane technique, i.e. inside a previously grafted membrane, because of a recurrence of the infection; and one patient was implanted with BAG-S53P4 during the second stage of a second induced membrane technique to avoid a new failure. At a follow-up of 16 months, all healed without any recurrence of the infection.
Discussion: Critical size bone defects caused by an open fracture or an active infection can usually be addressed by the induced membrane technique. However, some cases are at high risk of failure because of the occurrence or recurrence of an infection. In these cases, bioactive glass may help the surgeon to improve the rate of bone union.
Conclusion: BAG-S53P4 may be considered as bone graft in an induced membrane technique, especially when there is a high probability of occurrence or recurrence of a bone infection.

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Introduction

A critical sized bone defect is defined by a bone defect that is too wide for healing spontaneously or with standard cancellous bone graft. Even nowadays, it remains a challenging situation for a majority of orthopaedic and trauma surgeons [1]. Historically, different surgical solutions have been reported. The most reported remain open-air cancellous Papineau grafting [2], free vascularized fibular graft [3] and bone transport [4]. Recently, Masquelet et al. reported the use of a spacer of acrylic cement implanted inside the defect that creates an induced membrane with bone healing properties [5]. It was later reported that this spacer triggers a reactive membrane that has shown, both experimentally and clinically, bone creation properties after cancellous bone autograft [6,7].

However, since the first description of the principles of the induced membrane technique, those who used it realized that, while the technique seems quite simple, many factors play a role in the success [6]. Hence, the technique evolved and gained in complexity. Technical additions have also punctuated the experience, culminating today in a mosaic of possibilities, requiring a detailed program for each case treated. As infection is often one of the major causes for failure, adequate treatment of infection is paramount in this challenging field. In the induced membrane technique, recurrence is one of the major causes of primary failure. In case of a primary failure, therefore, the attitude remains discussed between doing it again, switching to another technique or even to amputate.

Other options may be possible if bioactive glass S53P4 (BAG-S53P4) is considered for that type of situations. In fact, BAG-S53P4 is synthetic, biocompatible and osteoconductive material. Its ability to integrate with bone and soft tissue was first described in in 1971 [8]. Since then, BAG-S53P4 has been shown to have antibacterial, osteostimulative and angiogenic properties [9–15]. Hence, these properties give BAG-S53P4 a preferred option when a bone substitute is considered to address bone defects due to infections. Based on the mentioned studies, the use of BAG-S53P4 in concurrence with antibiotic therapy showed significant potential in the treatment of osteomyelitis [16]. For these reasons, BAGS53P4 may be considered as an option to use in case of a failure or a high risk of failure of an induced membrane technique for a bone defect of septic origin.

In this study, we aimed to estimate the utilisation of BAG-S53P4 in the cases of induced membrane technique failed or with an anticipated high risk of failure. Our hypotheses were 1) that BAG-S53P4 was a safe bone substitute in an induced membrane in terms of material related complications; 2) that BAG-S53P4 was an effective bone substitute for long bone defects addressed with the induced membrane technique in terms of bone creation and recurrence of an infection.

Material and methods

Protocol and registration

We specified in advance the objectives, methods of analysis and inclusion/exclusion criteria for this study. We subsequently documented them in a protocol. We aimed to ascertain the quality of the study by using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist designed for case reports, cohort studies, and patient series. The STROBE statement is a list of guidelines developed by the STROBE initiative in order to increase the quality of observational studies [17].

General settings

We designed a retrospective analysis of cases gathered among several European Surgical Centres specialized in limb reconstruction. We considered every patient treated for a segmental bone defect of critical size that was addressed with the induced membrane technique and in whom a bioactive glass was used as a bone substitute during the whole process. We excluded any patient with an incomplete clinical chart and/or a follow-up lesser than one year.

Data retrieved

We retrieved information from the clinical chart of every included patient:

- Patient's characteristics: Gender (F/M), Age at diagnosis (Yrs), Height (Cm), Weight (Kg), Body Mass Index BMI (m/Kg2), Work status (Y/N), Active smoker (Y/N), American Society of Anaesthesiologists physical status classification or ASA Score [18].
- Analysis of each case: What was the indication for BAG in the induced membrane?
- Group of indication for BAG in the induced membrane: Primary course of induced membrane technique, Secondary course of induced membrane technique, Third stage of during a primary course of induced membrane.
- First stage of the induced membrane technique: Initial disease, Complete resection of the disease (Y/N), Size of the defect after bone debridement (mm), Index of resection (%; size of the defect / size of the total bone), Type of osteosynthesis, Antiobiotics in PMMA (Y/N), Post-operative cast (Y/N), Initial full weight-bearing (Y/N).
- Second or third stage of the induced membrane technique: Delay between the first and the second stage or between the second and the third stage (months), Change of osteosynthesis (Y/N), Type of osteosynthesis, BAG alone, BAG + autograft, BAG + other bone substitute, Post-operative cast (Y/N), Full weight-bearing (Y/N).
- Post-operative complications: Resorption of the graft material, Non-union, Fracture, Other.
- Final result: Primary bone union (Y/N), Delay before union (months), Secondary bone union (Y/N), Follow-up (months).

Furthermore, we retrieved orthogonal X-rays of the operated limb before the primary course of induced membrane technique, then after each following stage, and at last follow-up.

Types of endpoints measures

Our primary outcome was the rate of bone union. Bone union was defined as a bone continuity between the two segments of the initial bone defect, identified on two orthogonal X-rays. Our secondary outcome was the rate of recurrence of infection. A recurrence of infection was defined as the recurrence of any sign of osteomyelitis – such as fever, local inflammation, swelling, drainage, etc…- after the surgery. Finally our third outcome was the rate of complication directly related to the BAG. We defined a complication directly related to the BAG as any incident directly related to the bone substitute.

Summary measures

We report dichotomous outcomes as counts and proportions. Given the anticipated small size of the sample that we gathered, we specifically opted not to perform any statistical analysis.

Additional analysis

We conducted no post-hoc analysis.

Ethical considerations

We informed all the patients before the beginning of the study and received the permission to use their data for this report.

Results

Patients included

Eight patients were eligible to inclusion. None of them met an exclusion criterion. Hence, eight patients were included for analysis. Three of the patients were women and five were men. Mean age was 43 years (16-82; Standard deviation 23). Mean height was 171 cm (162-184; SD 7), mean weight was 69 kg (60-85; SD 8) and Body Mass Index was 23,39 m/Kg2 (21,9-25,1; SD 1,22). Four patients were employed before the initial trauma. Three patients were actively smoking before the trauma and all of them continued to smoke during the process. Mean ASA score was 1.4 (1-2, SD 0.5). Three patients were treated for an acute open fracture, two for a chronic infectious non-union, two for a chronic non-union and one for a chronic osteomyelitis. Five patients have been included after a primary course of Induced Membrane Technique, one has been included for a secondary course of Induced Membrane Technique, and two have been included after a third stage during a primary course of Induced Membrane Technique.

First stage of the technique

During the first stage of the Induced Membrane technique, all the patients but one had a complete resection of the disease. Mean size of the defect after bone debridement was 68 mm (40-100, SD 23) which represented a mean index of resection of 19% (10-25, SD 0.05). Five patients had an osteosynthesis by an intramedular locked nail, 2 a single plate and one a double plating. All patients had a spacer made of PMMA mixed with antibiotics. Three patients had a post-operative cast and two of them were authorized a full weight bearing on the cast.

Second stage of the technique

For the patients who underwent a single Induced Membrane program, the mean time during the two stages was 3 months (1.5-7; SD 2.11). In one case, the initial osteosynthesis was modified by addition of a compression plate to an intramedullary nailing of the tibia (Fig. 1). Two patients were grafted with BAG only and three had a mixture of autograft and BAG. In all the cases, the bioactive glass used was BAG-S53P4 (BonAlive Biomaterials Ltd, Turku, Finland) (Figs. 2–5). A post-operative cast was added in one case. Two patients, the same as the first stage, were authorized a full weight-bearing.

Third stage of the technique

Two patients underwent a third stage of the Induced Membrane technique because of a failure after the second stage. The third stage was performed at 11 and 21 months after the second one. In the two cases, the initial osteosynthesis was modified by a change of the previous intramedular nail. In the two cases, only BAG-S53P4 was used.No post-operative cast and no weight bearing was authorized.

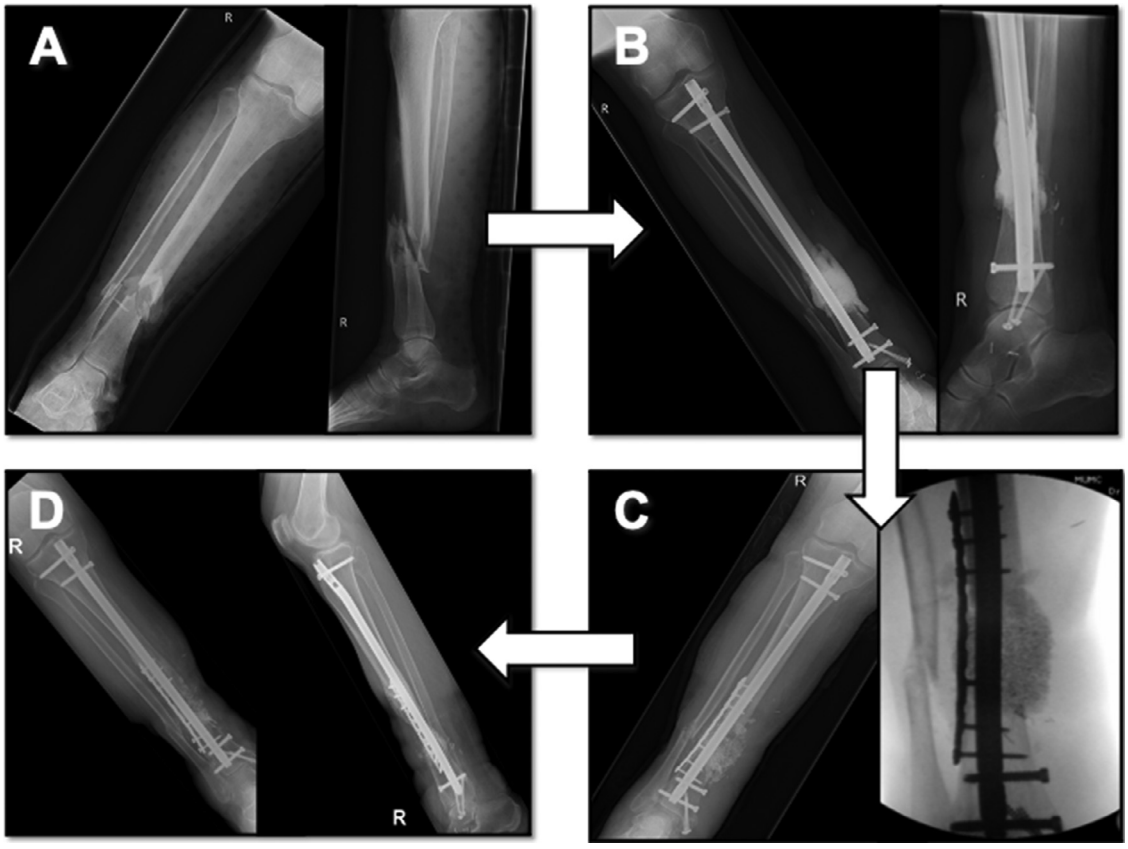

Fig. 1. Example of the use of BAG for an open right tibia fracture addressed with an induced membrane and with a high risk of infection (A: pre-operative X-Rays, B: First stage X-Rays, C: Second stage X-Rays, D: X-Rays at 1 year last follow-up).

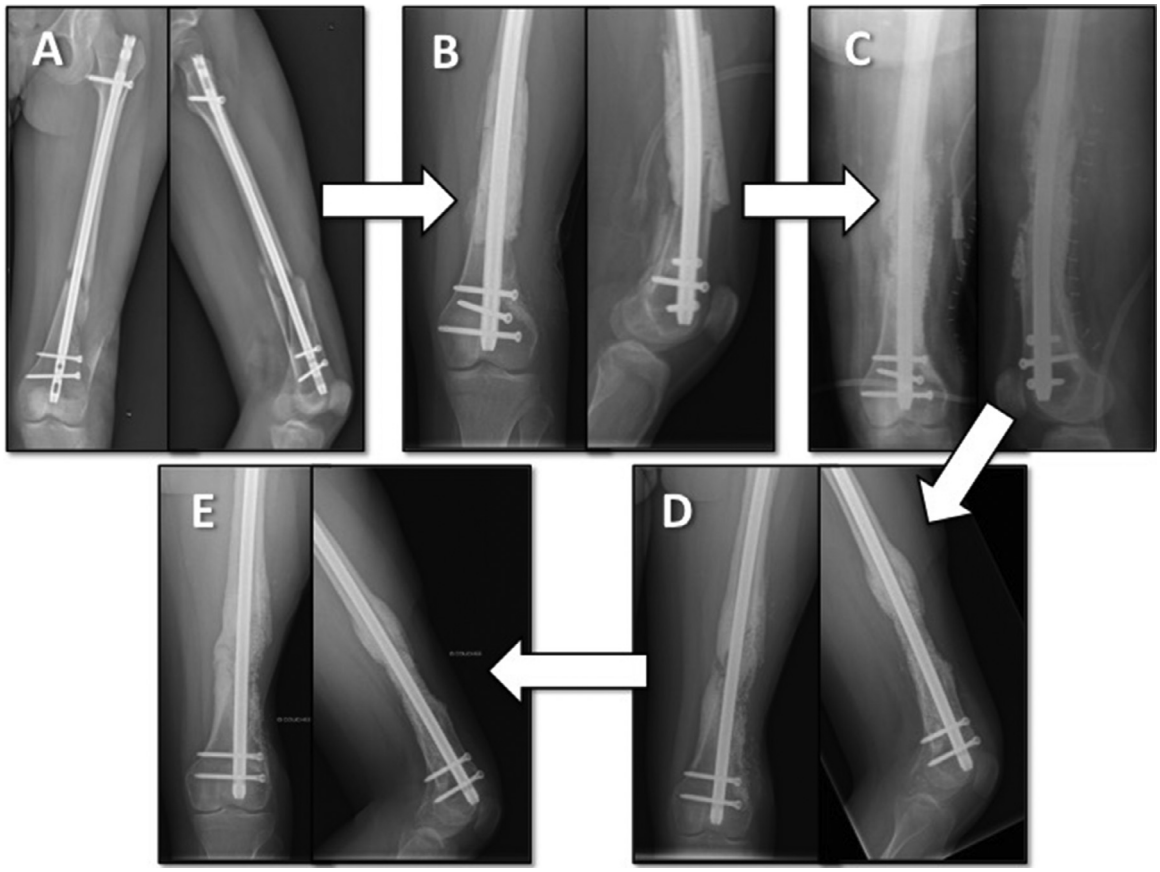

Fig. 2. Example of the use of BAG for a third stage of induced membrane technique following a recurrence of the infection after the second stage in a left femoral defect (A: pre-operative X-Rays, B: First stage X-Rays, C: Third stage X-Rays at 11 months, D: X-Rays at 1 year, E: X-Rays at 2 years follow-up).

Outcomes reported

After a mean follow-up of 17 months (6-30, SD 8.9), all the patients but one had bone union. However, one patient presented a weak continuity between the host tibia and the consolidated graft at its proximal aspect mimicking a docking side issue as encountered in the bone transport techniques. The delay before bone-union was 7.14 months (3-20; SD 5.98). No infection recurred. No complication directly related to the bioactive glass was reported.

Discussion

In this multicentric study, we estimated retrospectively the utilisation of BAG inside an induced membrane for severe bone defect with high risk of infection. Hence, we could confirm our hypotheses by the results reported. First, BAG-S53P4 is a safe bone substitute in terms of material related complications when used in an induced membrane. Second, BAG-S53P4 is an effective bone substitute, used alone or in association with autograft, when used in an induced membrane.

Knowing that long bone infection remains a challenging situation for the orthopaedic surgeon, these results should be of great interest. In fact, despite a treatment comprising a thorough debridement and administration of antibiotics for a certain time, some cases of long bone infection may still recur. When a bone defect is present, this risk may be higher [16]. For that reason, several surgical techniques have been designed. One of the more effective seems to be the induced membrane technique. However, the number of clinical situations is infinite and in some cases, the surgeon may face a recurrence of infection or may fear a high risk of such recurrence even after one surgery. In such cases, he may be tempted to add bioactive glass in an induced membrane. In this study, we identified several of these situations: first, during a primary program of induced membrane to avoid the “moist sand effect” because of the size of the defect; second, during a program of induced membrane because of a high risk of infection (for instance, induced membrane for open fracture); third, because the second stage of the first induced membrane program failed for infection; and finally to ensure no infection for a second induced membrane program after failure due to infection recurrence.

In such cases of high risk of infection, we think that bioactive glass is a tempting option as graft material. On a biological aspect, bioactive glass is a good option for filling a biological chamber created to address the bone defects related to bone infection or to open fractures with a high risk of infection. Indeed, it combines several advantageous properties: it is anti-microbial, osteoconductive and angiogenic material [10]. For the anti-microbial aspect, the initial leaching of alkali and alkaline ions lead to a rapid increase in pH around the glass. This basicity depends on the composition of the glass: BAG-S53P4 that was used in all the cases gathered has shown an increased pH value up to 11.65 in a simulated body fluid [19]. This increase of pH, and the subsequent osmotic effect caused by dissolution of the glass, have been suggested to partly explain the antibacterial properties observed for BAGs [20]. This antibacterial effect has been observed in vitro for all pathogens tested, including the most important aerobic and anaerobic pathogens, as well as very resistant bacteria [11,21]. For the osteoconductive aspect, the process leading to bone bonding is a sequence of reactions in the glass and at its surface. In fact, implantation of glass is followed by an exchange of Na+ in the glass with H+ and H3O+ from the surrounding tissue, leading to the formation of silanol (SiOH) groups at the glass surface. After re-polymerization, a SiO2-

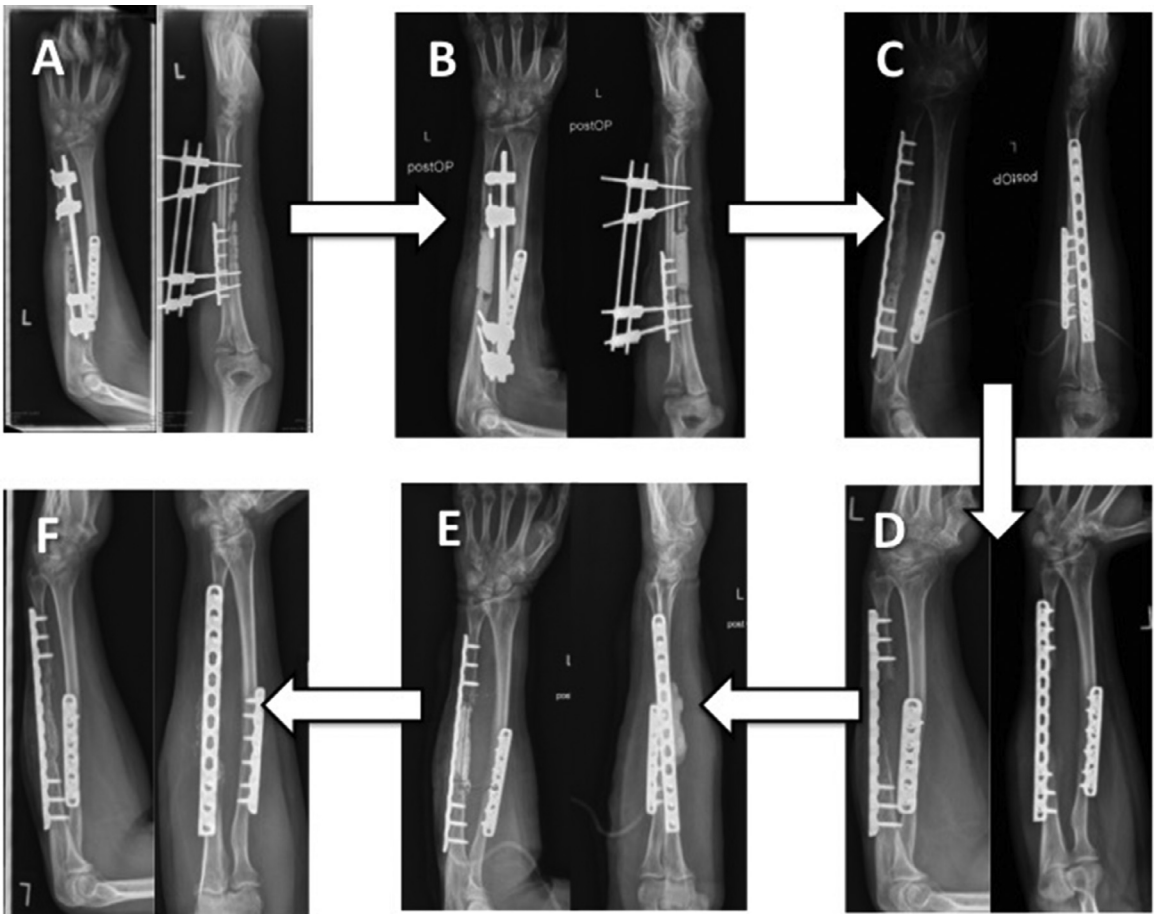

Fig. 3. Example of the use of BAG for a second course of induced membrane technique following a failure of the first course in a left ulna midshaft bone defect (A: pre-operative X-Rays, B: First stage X-Rays of the first course, C: Second stage X-Rays of the second course at 3 months, D: Control 1 month later showing the lysis of the graft due to early infection, E: X-Rays at 9 months after the second stage of the second course).

rich layer is formed. Due to migration of Ca2+ and PO34− groups to the surface and crystallization, a CaO-P2O5 hydroxyapatite (HA) layer is formed on top of the Si-rich layer. Finally, cell interactions with the HA layer subsequently initiate the bone forming pathway. Once the HA layer has formed, absorption of growth factors occurs, followed by the inward migration of osteoprogenitor cells which trigger the synthesis of extracellular matrix and new bone formation [22–24]. For the angiogenetic aspect, bioactive glass has been shown to stimulate release of angiogenetic growth factors and to promote angiogenesis [12]. The proangiogenic potential of soluble products of BAG-45S5 has been determined by examining the capacity to induce endothelial cell proliferation and up-regulation of VEGF production and results indicated that BAG-45S5 possesses a robust proangiogenic potential [25]. Finally, Björkenheim et al. showed recently in a preclinical rabbit model that bone morphogenic protein expression and bone formation are induced by bioactive glass S53P4 scaffolds in a one-stage induced membrane model [26]. They concluded that induced membranes in the BAG-S53P4 scaffold group showed similar or superior expression of BMP-2, BMP-4 and BMP-7 compared with induced membranes in the PMMA group. This finding may prove to be a very important contributing factor in the healing and consolidation of the bone.

Despite these beneficial properties, is there certain limit of the use of BAG inside a biological chamber such as the induced membrane? First of all, BAG is not a “solution to everything” and several authors pointed out two risk factors of recurrence of infection when BAG is used: an un-properly filled cavity and a failure of skin coverage [16]. Lindfors et al. reported one case of recurrence of infection directly related to an un-properly filled cavity: the fact that the cavity had not been properly filled resulted in a formation of a haematoma and a subsequent infection [27]. Drago et al. analysed also their failed cases and suggested an insufficient filling of the bone defect [28]. But Drago et al. reported that the other two failed patients in their case-series shared soft tissue defects and that it might have impaired the outcome. Both of these patients were candidates to simultaneous flap coverage at the time of debridement but that had not been undertaken because direct closure was finally achieved. In spite of this, both suffered healing wound problem after surgery and one of them finally received a fascio-cutaneous flap, with resolution of the septic process, while the other refuses further surgery, in the presence of an intermittently draining fistula [28]. Furthermore, we want to add a satisfying bone vascularisation as a third risk factor of recurrence of infection from our experience. Indeed, a satisfying bone vascularisation will allow a good “cell homing” that will ensure a good bone formation. Finally, it seems mandatory to have a stable osteosynthesis when an induced membrane technique is used and that should not change even if BAG is the bone substitute [16].

We acknowledge several limitations to our study. First, it is a multicentric study but its design is based on a previous knowledge of several Surgical Centers specialized in Bone Infection. Given that this is not an official web of competence, there is a risk of selection bias. Second, the analysis of each case was retrospective. That implies an absence of control of any clinical aspect and it could lead to an interpretation bias. Third, the interpretation of the data was made by the surgeon following each case, which could lead

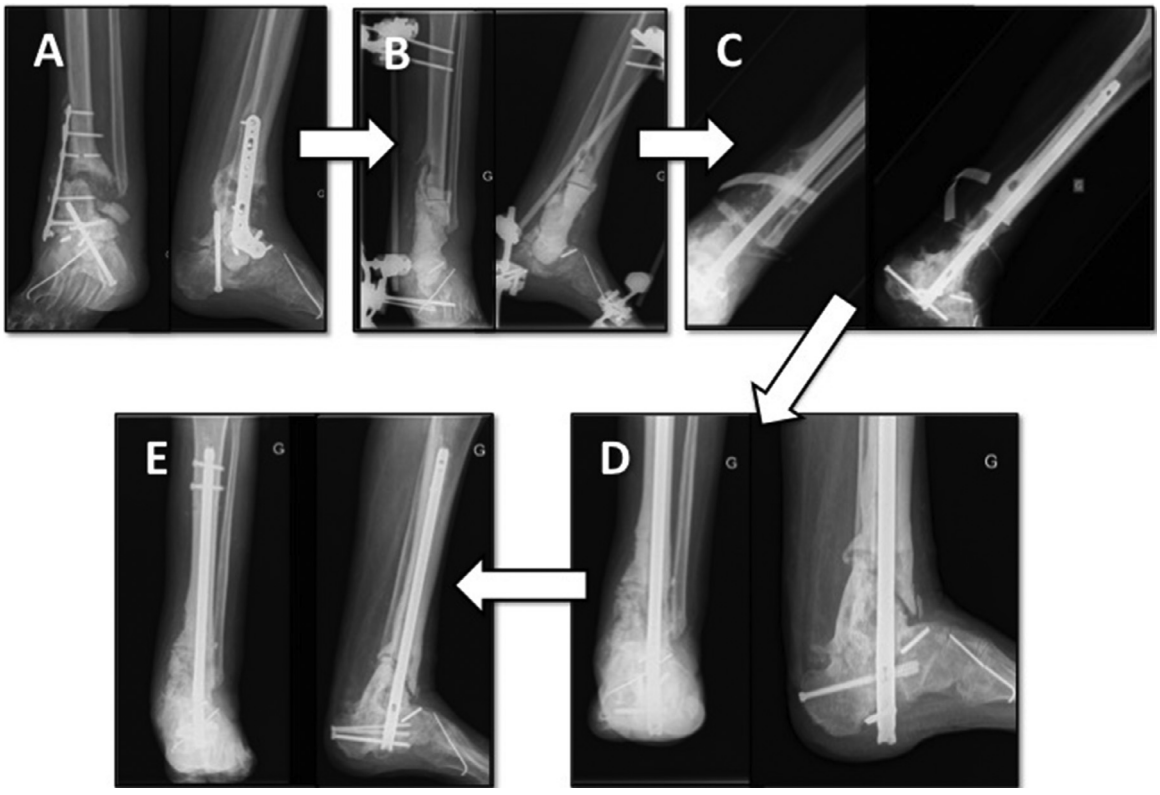

Fig. 4. Failure of the use of BAG in an induced membrane because of the recurrence of the infection in a left distal tibial bone defect (A: pre-operative X-Rays, B: First stage X-Rays, C: Second stage X-Rays 21 months after the first stage, D: X-Rays 3 months after BAG implantation, E: X-Rays at last follow-up of 2,5 years).

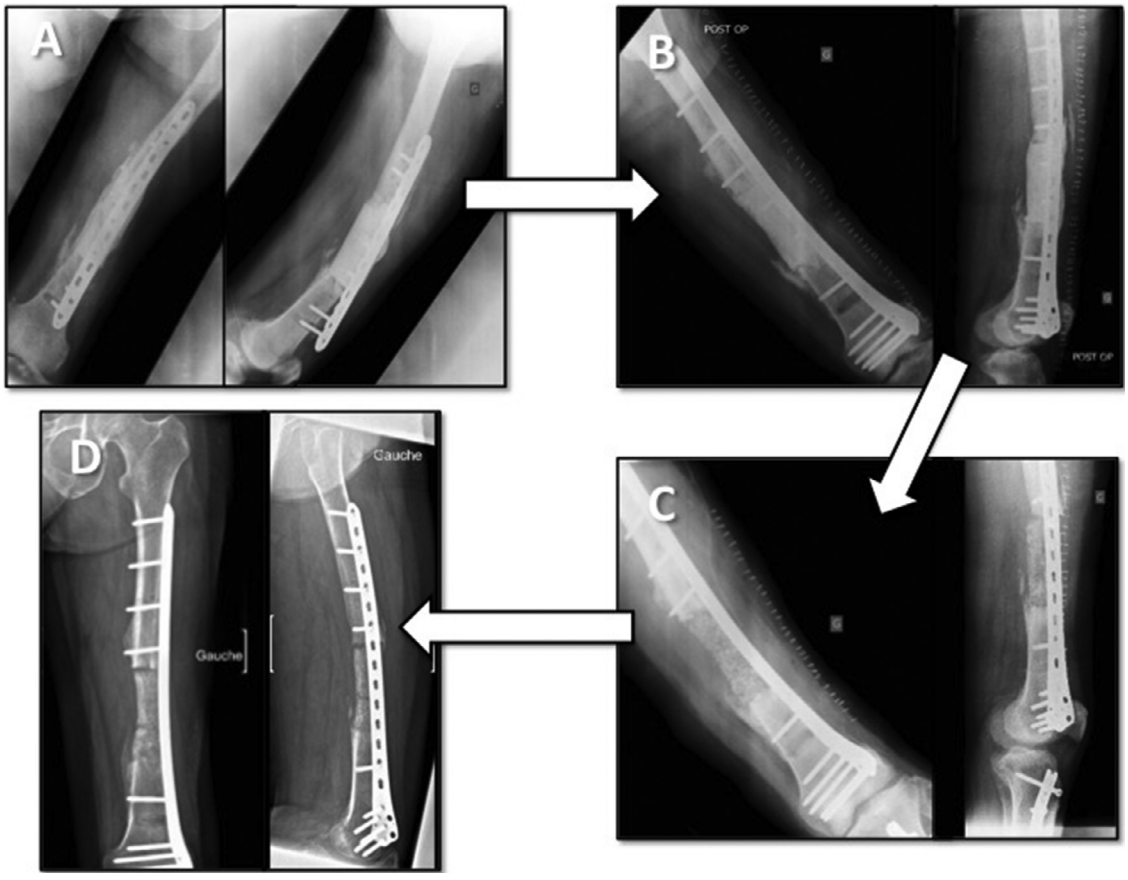

Fig. 5. Example of a satisfying bone creation but a "docking side" like effect at the proximal part of a long graft in a left distal femur (A: pre-operative X-Rays, B: First stage X-Rays, C: Second stage X-Rays 4 months after the first one, D: X-Rays 6 months after grafting).

to a bias of interpretation too. Finally, the follow-up is relatively short given the initial disease, which is known to potentially have recurrence even a very long time after the treatment. However, according to the International Society for Infectious guidelines on requirements of human trials on osteomyelitis, a favourable outcome is achieved when the patient is clinically free of disease at the end of the follow-up. According to these guidelines, clinical follow-up trials should last for a minimum of 1 year [29].

In conclusion, we found that bioactive glass S53P4 might be considered as bone graft in an induced membrane technique, especially when there is a high probability of occurrence or recurrence of a bone infection.

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