Osteostimulation
Inhibition of Bacterial Growth
Bioactive Bone Bonding
Natural Hydroxyapatite Formation
Osteostimulation*
Bone Regeneration

Medical education | ENT, CMF & Neurosurgery
MECHANISM OF ACTION

BonAlive® granules (bioactive glass S53P4) is a CE-marked class III medical device that is used in surgical procedures to regenerate bone. BonAlive® granules is osteostimulative* which means that it activates genes responsible for bone formation in osteogenic cells. It also has the special property of effectively inhibiting bacterial growth, which makes it a very unique material for regenerating bone.

Inhibition of Bacterial Growth
In contact with body fluids bioactive glass works by leaching out ions leading to an alkaline environment (high pH) and increased osmotic pressure. This mechanism has been shown to effectively inhibit bacterial growth.

BonAlive® granules Composition:
- 53% SiO₂, 23% Na₂O, 20% CaO, 4% P₂O₅

BonAlive® granules Indications:
- Bone cavity filling in cranio-maxillofacial area including the jaw
- Frontal sinus obliteration after severe chronic sinusitis or fractures in the frontal bone area
- Mastoid cavity obliteration and nasal cavity narrowing

Bone Bonding and Osteointegration
The surface reactions develop a silica gel layer on the bioactive glass, which attracts the Ca and P that has been released from the granules. The precipitated CaP crystallizes to natural hydroxyapatite, which is similar to the mineral component of bone. The newly formed natural surface will promote bone bonding and osteointegration.
INHIBITION OF BACTERIAL GROWTH

One of the most striking features of BonAlive® granules is its ability to inhibit bacterial growth. This phenomenon has been evidenced with more than 50 clinically relevant aerobic and anaerobic bacterial species through in vitro studies, and indirectly by empirical observation of patient data over the past 15 years.

Chronic bone infections play a large role in surgery as the infection can be difficult to eradicate and might require several operations. Antibiotic resistance has become an increasing threat and new tools that are not based on antibiotics can bring significant benefits in fighting chronic bone infections. The efficacy of BonAlive® granules towards methicillin-resistant (MR) Pseudomonas aeruginosa, Staphylococcus aureus (MRSA), Staphylococcus epidermidis (MRSE) has been tested and proven effective.

Mechanism

The bacterial growth inhibiting effect of BonAlive® granules is based on two simultaneous processes that occur when the bioactive glass reacts with body fluids.

1. Sodium is released from the surface of the bioactive glass and induces an increase in pH (alkaline environment), which is not favourable for the bacteria.

2. The released Na, Ca, Si and P ions give rise to an increase in osmotic pressure due to an elevation in salt concentration, i.e. an environment where the bacteria cannot grow.

These two mechanism will together effectively inhibit the adhesion and colonization of bacteria on the granule surface.

References

BonAlive® granules is effective in inhibiting bacterial growth of more than 50 common bacteria species (including MRSA, MRSE).

### Gram Positive Bacteria
- Bacillus cereus
- Bifidobacterium adolescentis
- Clostridium difficile
- Clostridium perfringens
- Clostridium septicum
- Corynebacterium ulcerans
- Enterobacter cloacae
- Enterococcus faecalis
- Enterococcus faecium
- Eubacterium lentum
- Listeria monocytogenes
- Micrococcus sp.
- Mycobacterium tuberculosis
- Peptostreptococcus anaerobius
- Peptostreptococcus magnus
- Propionibacterium acnes
- Propionibacterium propionicus
- Staphylococcus aureus
- Staphylococcus epidermidis
- Staphylococcus hominis
- Staphylococcus lugdunensis
- Streptococcus agalactiae
- Streptococcus mutans
- Streptococcus pneumoniae
- Streptococcus pyogenes
- Streptococcus sangui

### Gram Negative Bacteria
- Acinetobacter baumanii
- Bacteroides fragilis
- Bacteroides thetaiotaomicron
- Chryseobacterium (former Flavobacterium) meningosepticum
- Enterobacter aerogenes
- Enterobacter amnigenus
- Escherichia coli
- Fusobacterium necrophorum
- Fusobacterium nucleatum
- Haemophilus influenzae
- Klebsiella pneumoniae
- Moraxella catarrhalis
- Neisseria meningitidis
- Pasteurella multocida
- Porphyromonas gingivalis
- Prevotella intermedia
- Prototella intermedia
- Proteus mirabilis
- Pseudomonas aeruginosa
- Salmonella typhimurium
- Shigella sonnei
- Veillonella parvula
- Yersinia enterolitica

### Methicillin-resistant bacteria
- Pseudomonas aeruginosa
- Staphylococcus aureus (MRSA)
- Staphylococcus epidermidis (MRSE)

The images illustrate the impact of S53P4 on methicillin-resistant Staphylococcus aureus, Klebsiella pneumoniae and Acinetobacter baumanii. The inhibition of bacterial growth can be seen as changes in the morphology of the bacteria; deformation of the cells and hole formation in the cell membranes.
OSTEOINTEGRATION AND OSTEOSTIMULATION*

An osteoconductive material functions as a scaffold that allows bone growth on its surface or into its three-dimensional structure. BonAlive® granules is osteoconductive in nature, providing a supportive material for the osteoblast cells during bone formation. As a result of the osteoconductive process, bone grows onto and between the bioactive glass granules. Furthermore, the bioactive glass granules have been proven to activate a biological process that stimulates bone regeneration in a fashion far superior to mere osteoconductive materials. This is defined as osteostimulation*.

“*The bioactive glass surface is not only conductive but also osteoproducive in promoting migration, replication, and differentiation of osteogenic cells and their matrix production.”

Virolainen et al. 1997

1 Day

Hydroxyapatite starts to form on BonAlive® granules surface.

1 Week

Hydroxyapatite covers BonAlive® granules surface.

6-12 Weeks

BonAlive® granules bond to bone and stimulate new bone formation (osteostimulation*).
Formation of Natural Hydroxyapatite and Osteointegration

The bioactive surface of the BonAlive® granules is characterized by its ability to attach firmly to living tissue, facilitate tissue growth and bond chemically with surrounding bone. Osteogenic cells, such as osteoblasts and osteoclasts will be stimulated by the released Si and Ca and the natural hydroxyapatite surface. Subsequently the bone formation pathway will be initiated.

References

Histological 20μm-thick section from the mastoid area at 3 months after BonAlive® granules implantation (human biopsy).

Osteostimulation*

The mechanism of bone regeneration with bioactive glass has been demonstrated to be based on both **surface-mediated** (natural hydroxyapatite surface) and **solution-mediated** (release of Si and Ca) processes. The effect is seen on a cellular level as promotion of particular cell stages of the osteogenic cell lineage through specific gene activation. This active role in osteogenesis has been defined as osteostimulation*. In vitro and preclinical studies with BonAlive® granules give evidence that it acts as an osteostimulative* material.

BonAlive® granules Plays an Active Role in:

- recruitment and differentiation of osteogenic cells
- promotion of osteogenic cells to increase the remodeling rate of bone
- activation of specific genes in osteogenic cells as a response to ion dissolution and the natural HA surface

References


*non-osteoinductive
The radio-opaque nature of the bioactive glass brings significant benefits. The BonAlive® granules can be visualized with imaging during surgery and the progression of the healing can be followed post-operatively.

The following imaging has been produced after mastoid obliteration to detect residual cholesteatoma. In all CT scans and MRI sequences a cholesteatoma can easily be detected since the appearance of the BonAlive® granules is completely different from the appearance of cholesteatoma. The white arrows point to where the BonAlive® granules are applied.
Canal-wall-down (CWD) procedures can lead to burdensome postoperative treatment. The disadvantages of CWD cavities are associated with the need for frequent cleaning of the cavity due to debris accumulation or infections and difficulties in using hearing aids. Occasionally revision surgery to decrease or eliminate the mastoid cavity with the aim of eradicating the infection is an alternative.

Several long term studies have shown that mastoid cavities with continuous infections and cleaning problems can be obliterated with BonAlive® granules. The BonAlive® granules have been used for more than 15 years with success for mastoid obliteration. The unique bacterial growth inhibiting feature and slow resorption profile of BonAlive® granules give distinct advantages when used to obliterate discharging and chronically infected mastoid cavities. In addition, the osteostimulative* property of BonAlive® granules supports new tissue formation in the cavities.

**References**


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**BonAlive® granules Indication**

- Mastoid cavity obliteration

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**References**


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**BonAlive® granules Indication**

- Mastoid cavity obliteration

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**References**


Surgical Technique of Mastoid Obliteration

1. Retroauricular incision 1 cm from the ear base. Skin from the mastoid cavity is elevated from the walls of the cavity to form new skin for the posterior canal wall. All ridges are removed and the cavity is cleaned with a diamond burr.

2. Pieces of cartilage are placed in the bottom of the cavity along the ear canal wall. The cartilage supports the new skin of the ear canal and will prevent BonAlive® granules from migrating into the ear canal. If needed, a layer of fascia from the temporal region can be placed between the skin and the cartilage to provide additional support for the canal wall.

3. The cavity is partially obliterated with moistened BonAlive® granules during this stage, since the external auditory canal needs to be shaped and tamponed first.

4. The posterior ear canal wall is shaped from the external ear canal according to the desired anatomy. Silicon sheets are inserted along the external ear canal and the tampons are placed to give support to the ear canal wall.

5. The mastoid is filled up with moistened BonAlive® granules to the level of the cortical bone. If suitable cartilage pieces are available they can be placed on top of the granules. The musculoperiosteal flap will be placed to cover the granules and the incision is sutured.

6. According to clinical experiences, edematous swelling can be reduced and excess fluid can be evacuated by applying a vacuum drain into the area that has been obliterated with BonAlive® granules. The drain can be removed within a few days postoperatively, when the vacuum maintains for 8–12 hours.
Obliteration of a Chronic Ear with Effusion and Caloric Stimulus

Patient: A 46-year old male with a radical cavity in the left ear. The patient was operated 2 years previously, which resulted in a chronic ear with recurrent effusion, incomplete cleaning and caloric stimulus. It was difficult for the patient to wear a hearing aid causing effusion.

Preoperative Finding: There was no overview to the terminal cell with a 30° endoscope and the external ear canal had a very narrow entrance.

Operation: With a retroauricular incision a tympanoplasty/mastoidplasty was performed. A massive cholesteatoma epithelium was removed from the terminal cell. The dura middle fossa cranii was visible. The mastoid and middle ear area was thoroughly cleaned from scar tissue. The incus was absent and the mobile stapes (type III) was covered with thick cartilage. The cartilage was removed and a VARIAC-Titanium prosthesis (partial 2.5) implanted with a thin plate of cartilage underneath the tympanic membrane. The visible dura was covered with perichondrium. Obliteration of the mastoid was performed with 5 cc BonAlive® granules, covered by overlapping thinned pieces of cartilage from the cavum conchae after the meatoplasty and fascia from the m. temporalis. The attic was only filled with cartilage. No postoperative treatment with antibiotics was given.

Clinical Outcome: At 3 weeks postoperatively the silicon sheets and the package (tampons) were removed from the external ear canal. An incomplete epithelization of the posterior ear wall was observed. The external ear canal (meatus) was treated with ear drops. At 5 months postoperatively the skin of the external ear canal (meatus) was slightly reddish and swollen.

At 14 months the meatus had healed well presenting a normal anatomy. At 3.5-year follow-up the patient was fully healed and presented a normal ear.
Obliteration of an Old Chronically Infected Mastoid Cavity

Patient: A 57-year old male (bank employee) who underwent a radical mastoidectomy in the left ear at the age of 14. The patient suffered from continuous secretion/effusion with pain requiring frequent treatment by an ENT-specialist. The patient was not able to use a hearing aid.

Preoperative Finding: The patient had a cavity with granulation in the sinus dura angle. There was no control of the mastoid/terminal cell with a 30° endoscope.

Operation: With a retroauricular incision a mastoidplasty was performed. The mastoid was cleaned and all granulation tissue was removed. The dura medial fossa cranii was visible, the epithelium was removed from the attic (malleus head and incus were absent) and the middle ear was kept untouched. The mastoid was obliterated with 4.5 cc BonAlive® granules and covered with overlapping thinned pieces of cartilage from the cavum conchae and fascia from the m. temporalis. No postoperative treatment with antibiotic was given.

Clinical Outcome: At 2 months postoperatively the meatus was still reddish and swollen. The external ear canal (meatus) was treated with ear drops (consisting of dexamethasone, neomycin and polymyxin) for 2 weeks. At 5 months the meatus had healed well presenting a normal anatomy and the patient could wear a hearing aid without problems.
Obliteration of a Radical Mastoid Cavity with Cholesteatoma

Patient: A 76-year old female who had undergone a tympanoplasty (canal wall down) and meatoplasty (cartilage) of her left ear 40 years ago. Her condition became chronic with recurrent secretion in her left ear, which resulted in frequent intervals of treatment (every 2 weeks). Wearing a hearing aid also caused problems.

Preoperative Finding: It was difficult to get an overview of the mastoid endoscopically. A posterior wall that had been partially reconstructed with cartilage and a retraction to the attic could be visualized.

Operation: With an endaural incision a tympanoplasty/mastoidplasty was performed. Excessive cholesteatoma was removed and thorough cleaning of the mastoid was performed. In the middle ear, scar tissue was present and the incus and malleus heads were absent. The stapes was mobile (Type III) and it was interpositioned with a thin plate of cartilage. The mastoid and attic was obliterated with 3.5 cc BonAlive® granules and covered with 3 thinned pieces of cartilage from the tragus and fascia from the m. temporalis. No postoperative treatment with antibiotic was given.

Clinical Outcome: At 3 weeks postoperatively the silicon sheets and the package (tampons) were removed from the external ear canal. An incomplete epithelization of the posterior ear wall was observed. The external ear canal was treated 2 x with merocel sticks and eardrops (ciprofloxacin, twice a day), for 3 weeks.

At 6 months postoperatively the skin of the external ear canal (meatus) was reddish. At 14 months healing had progressed well but showed a slight retraction towards the attic. At 24 months the meatus was normal and the patient had no problems wearing a hearing aid.
Several long term studies, extending over 10 years of patient follow-up, have shown that BonAlive® granules generate outstanding clinical results in bone cavity filling applications in the cranio-maxillofacial area. The main applications of BonAlive® granules are filling of benign bone tumor cavities, filling of the osteotomy site in bilateral sagittal split osteotomies and fronto-orbital trauma. The solid nature of BonAlive® granules provides specific benefits, such as allowing the granules to be impacted into the bone defect. The granules maintain their volume effectively, hence they do not shrink or expand. BonAlive® granules produces a high and balanced local bone regeneration by stimulating new bone formation through osteostimulation*.

BonAlive® granules Indication

- Bone cavity filling in cranio-maxillofacial area including the jaw

References


*non-osteoinductive

Courtesy of Dr. Patricia Stoor
Helsinki University Hospital, Finland
Follicular Cyst in the Mandible

**Patient:** 30-year old female with follicular cyst.

**Operation:** 6 cc of BonAlive® granules was used to fill the defect.

X-ray image showing the cyst with total lack of posterior bone support for the second molar.

Surgical removal of the wisdom tooth and the cyst (20x15x30 mm). Nervus alveolaris inferior was exposed and covered with a collagen membrane.

The second molar was saved and the defect was filled with 6 cc of BonAlive® granules.

The BonAlive® granules were covered with collagen membrane and the wound was closed.

**Outcome:** At 18 months postoperatively the area had healed and the posterior bone support for the second molar had been successfully recovered.

Histological section from the implanted area at 2 years after BonAlive® granules implantation. The arrow indicating residual granules with surrounding bone tissue.
Bilateral Sagittal Split Osteotomy (BSSO) Surgery

**Patient:** 45-year old female with mandibular retrognatia.

**Operation:** BSSO with a 10 mm mandibular advancement, 2.5 cc of BonAlive® granules was used for grafting on each side.

Pre-op X-ray shows the abnormal posterior positioning of the mandibula.

Clinical image of defect after sagittal split osteotomy and fixation with mini plate and mono cortical screws.

Filling of the osteotomy site with BonAlive® granules and application of tissue glue.

Immediate post-op X-ray shows the right positioning of the mandibula.

**Outcome:** At 12 months postoperatively the follow-up showed uneventful healing with a normal contour of the inferior mandible border.
Most conditions of the frontal sinus requiring surgery can be treated successfully by endonasal or nasofrontal duct reconstruction procedures. However, in certain difficult cases, optimal exposure of the entire frontal sinus area is essential. Frontal sinus obliteration can be a treatment alternative for such frontal sinuses.

The unique bacterial growth inhibiting feature of BonAlive® granules gives distinct advantages in areas that are postoperatively prone to infection.

**BonAlive® granules Indication**

- Frontal sinus obliteration after severe chronic sinusitis or fractures in the frontal bone area

**References**


Severe Mucopyocele in Frontal Sinus Area

Patient: A 59-year old male who developed an increasing soft and tender expansion on the left forehead. The patient suffered from headache and diplopia in the left gaze. He had been hit by a small metal fragment in the left frontal area of the head from soldering. Preoperatively the patient was treated with azithromycin 500 mg/week and methylprednisolone 5 mg/day.

3D illustration showing the effects of complicated mucopyocele in frontal sinus, orbita and frontal lobe.

Mucopyocele intraoperatively presenting a large amount of pus. The area was throughly debrided from necrotic tissues before the reconstruction.

CT illustration showing mucopyocele in frontal sinus, orbita and frontal lobe.

Filling of the frontal cavity with 25 cc BonAlive® granules and closing the frontonasal duct with a BonAlive® plate.
Clinical Outcome: At 2 months the patient had made an excellent recovery. The bacterial cultures were negative.

At 5 months ENT-doctors performed as planned a FESS procedure to widen the maxillary sinus ducts.

At 2 years and 8 months follow-up the patient was symptom free and had returned to work. No signs of infection was shown on the MRI.
REFERENCES

Mechanism of Action (Osteostimulation*)


Inhibition of Bacterial Growth


*non-osteoinductive
Frontal Sinus Surgery


Mastoid Surgery


Dental Surgery


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- **Small Applicator**
- **Large Applicator**

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<td>13140</td>
<td>0.5-0.8 mm (Small)</td>
<td>10 cc</td>
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INSTRUCTIONS FOR USE

Step 1.
- Peel open the pouch (start from the corners) and aseptically remove the sterile tray (see Figure 1).
- Detach the applicator from the tray
- Note that the pouch provides a sterile barrier to the device.

Step 2.
- Moisten the granules by injecting sterile physiological saline slowly through the cap membrane (see Figure 2).
- Make sure the granules are evenly moistened. The applicator can be turned upside down or tapped to allow the saline to moisten all granules.
- Note: saline injection can cause increase in pressure inside the applicator unless the excess pressure is released e.g. with the injection needle.

Step 3.
- In order to prevent spilling of the moistened granules from the applicator keep the cap facing upwards.
- Unscrew the cap (remove the stopper) and screw the shovel tightly onto the applicator body (see Figure 3).

Step 4.
- Turn the applicator to a horizontal position, and push the plunger rod to slide the moistened granules onto the shovel. Move the applicator to the defect site and implant the moistened granules from the shovel into the defect with the aid of a sterile instrument (see Figure 4).
- (Alternatively, if the shovel is not used, turn the applicator over a sterile cup, push the plunger rod to slide the moistened granules into the cup and subsequently perform the implantation with a sterile instrument.)
- Avoid dropping the granules outside the bone defect. Misplaced granules must be removed.

For complete instructions for use, see package insert.
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