A randomized prospective clinical trial comparing OsteoActivator-P coated membranes vs Collagen Membrane-P uncoated for accelerated localized alveolar ridge preservation.

Published: 07-05-2021
Last updated: 18-07-2024

Collagen barrier membranes are widely used for ridge preservation applications. Once an extraction socket is filled with a bone filler and covered by a collagen membrane, guided bone regeneration (GBR) is observed due to the barrier function of the...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON51997

Source
ToetsingOnline

Brief title
OsteoActivator-P for accelerated localized alveolar ridge preservation.

Condition

- Other condition

Synonym
loss of bone volume

Health condition

dentaal

Research involving
Human

Sponsors and support

Primary sponsor: Osteo-Pharma.B.V.
Source(s) of monetary or material Support: Osteo-Pharma B.V.

Intervention

Keyword: Alveolar ridge preservation, Collagen membrane, Guided bone regeneration, implant

Outcome measures

Primary outcome

• Significant increased bone formation as measured by histology.

• Occurrence of adverse events and adverse device effects

Secondary outcome

• Bone density and volume on cone beam computed tomography

• Investigator evaluation of handling.

• Probing depth, recession, bleeding upon probing

• Implant survival at 26 weeks and 52 weeks after implantation

• VAS scale questionnaire

• Implant Stability Quotient (ISQ) at implantation and after 12 weeks.

Study description

Background summary

Guided bone regeneration (GBR) is achieved by placing a collagen barrier membrane (e.g. obtained from porcine pericardium) onto a bone defect. GBR is a surgical procedure that uses barrier membranes with or without particulate bone

grafts and/or bone substitutes and is widely applied for dental implant therapies. In general, osseous regeneration by GBR is performed using CE certified collagen membranes and depends on the migration of pluripotent and osteogenic cells (e.g. osteoblasts derived from the periosteum and/or adjacent bone and/or bone marrow) to the bone defect site and exclusion of cells impeding bone formation (e.g. epithelial cells and fibroblasts). To accomplish the regeneration of a bone defect, the rate of osteogenesis extending inward from the adjacent bony margins must exceed the rate of fibrogenesis growing in from the surrounding soft tissue. After GBR procedures, bone regeneration follows a specific sequence of events. Within the first 24 hours after a bone graft, the graft material/barrier created space is filled with the blood clot which releases growth factors (e.g., platelet derived growth factor) and cytokines (e.g., IL-8) to attract neutrophils and macrophages. The clot is absorbed and replaced with granulation tissue which is rich in newly formed blood vessels. Through these blood vessels, nutrients and mesenchymal stem cells capable of osteogenic differentiation can be transported and contribute to osteoid formation. Mineralization of osteoid forms woven bone, which later serves as a template for the apposition of lamellar bone. This transformation of primary sponge work would eventually constitute both compact and reticular bone with mature bone marrow. These events occur 3 to 4 months post-surgery. A pericardial collagen membrane provides the optimal condition for GBR by simultaneously limiting the ingrowth of epithelial cells and facilitating the generation of a blood clot (due to bleeding at the site). This provides the optimal conditions for mesenchymal cells to differentiate into active osteoblast cells due to the barrier function of the membrane. The principal mode of action of a collagen membrane is therefore a barrier membrane that shields against epithelial cell ingrowth from the surroundings of the fracture and that retains and guides, in a mechanical way, the new structures that will differentiate into a new bone. Unlike so-called microfibrillar collagen, which is a partially water-insoluble acid salt of purified porcine corium collagen and capable to directly activate platelet aggregation (Sundaram & Keenan, 2010), no interaction between the (pericardial) collagen membrane and blood platelets has been described in the literature. As such there is no indication that there is a pharmacological process initiated by the membrane. Also, no immunological or metabolic actions have been ascribed to a (pericardial) collagen membrane in the literature (Elgali, et al., 2017) (Lee & Kim, 2014) (Stoecklin-Wasmer, et al., 2013) (Dimitriou, et al., 2012) (Bunyaratavej & Wang, 2001) (Schwartzmann, 2000) (Wang & Carroll, 2000).

The use membranes for GBR is widely used in the field of periodontal bone regeneration, not only for reconstructive surgery but most importantly to create a sufficient amount of bone to allow for osteointegration of dental implants, often in combination with bone grafts or bone graft substitute. Following teeth extraction, healing of extraction sockets is impaired due increased resorption of bone in the socket, applying the principle of GBR in alveolar extraction sockets resulted in significant less vertical and horizontal bone loss compared to control sites of un-augmented extraction sockets (Iasella et al., 2003; Lekovic et al., 1998). Collagen membranes are

also applied for augmentation of the alveolar ridge if the amount of bone is insufficient for implant placement. Augmentation by GBR can either be applied before implant placement, creating sufficient stable bone for the implant integration or at the time of implant placement. Both approaches resulted in successful augmentation and increased success rates of implant placement over non-augmented sites (Parodi et al., 1998; Von Arx et al., 2006; Chiapasco and Zaniboni, 2009). GBR is also used to treat other dental defects, as intrabony defects, furcation defects or root coverage procedures. As a consequence, collagen membranes have become the standard of care in reconstruction of dental bone defects.

Attempts have been made to accelerate bone formation in the treatment of periodontal bone by the application of growth factors, either directly applied or loaded on membranes or bone graft substitute (Gothard et al., 2014; Carreira et al., 2014). These growth factors include recombinant human bone morphogenetic protein 2 (rhBMP-2), rhBMP-7, recombinant human growth differentiation factor 5 (rhGDF-5) and recombinant human platelet-derived growth factor-BB (rhPDGF-BB) and have been tested in a several dental procedures, including alveolar reconstruction, sinus augmentation, tooth extraction socket healing, implant guided bone regeneration, and periodontal bone repair (Gothard et al., 2014; Carreira et al., 2014). Despite the large number of studies conducted, no consensus has been reached on the clinical efficacy of growth factors in orofacial bone regeneration. A systemic review by Li et al. (2019) addressing this problem, indicate that all application of rhBMP-2 are insufficient in promoting tooth extraction socket healing, sinus augmentation or reconstruction of alveolar clefts as tested in randomized clinical trials. Only a marginal effect of rhPDGF-BB was suggested for tooth extraction socket healing (a non-significant 2.16% increase of new bone formation) (Geurs et al., 2014, Ntounis et al., 2015).

In this context, Osteo-Pharma intends to clinically evaluate the application of OsteoActivator coated pericardial membranes for periodontal bone regeneration. OsteoActivator coating consists of ancillary amounts of testosterone and alendronate encapsulated in PLGA. Both compounds have been extensively clinically tested and have authorized by the EMA and FDA for various applications. It should be mentioned though that the use of OsteoActivator-P membranes will not result in any systemic exposure of either testosterone or alendronate due to the use of ancillary amounts of these compounds. Testosterone activates bone forming osteoblast cells whereas alendronate inhibits bone resorbing osteoclast cells resulting in a net effect of bone growth and thereby improving the process of GBR.

The nonclinical package for OsteoActivator - P comprises pharmacodynamic studies to support proof-of-concept and local tolerance, and biocompatibility studies with the porcine pericardial membrane. Information on pharmacokinetic characteristics and the (systemic) safety profile of ancillary substances testosterone and alendronate is based on published data and has been included in the relevant sections of the Investigator Brochure (6). Information on the safety of PLGA applied as the carrier for the ancillary substances is likewise

based on published data.

Study objective

Collagen barrier membranes are widely used for ridge preservation applications. Once an extraction socket is filled with a bone filler and covered by a collagen membrane, guided bone regeneration (GBR) is observed due to the barrier function of the membrane, allowing implant placement after a certain time period. Due to the addition of a PLGA coating containing ancillary amounts of alendronate and testosterone to a collagen membrane, bone formation is stimulated, which is expected to further accelerate GBR allowing implants to be placed at an earlier timepoint.

Study design

This is a prospective, randomized, standard of care controlled clinical trial.

Intervention

In this study, surgery and placement of a collagen membrane are considered standard of care. All subjects will receive standard of care. In the context of this study, the application of a collagen membrane, whether coated (experimental) or non-coated (control) is considered an intervention.

Study burden and risks

Currently, based on the data available and control measures defined, no risks have been found to be unacceptable in the context of a first in human clinical trial. Based on the data described in the IB it is concluded that (i) no adverse effects were observed in the biocompatibility study, (ii) the risk of clinically relevant pharmacokinetic drug interactions is estimated to be negligible, (iii) preclinical studies revealed no adverse effects as determined by detailed histology and (iv) the risk of adverse systemic effects related to the ancillary substances is estimated to be minimal under the proposed conditions of clinical use.
OsteoActivator-P is potentially beneficial to dental ridge preservation and is not associated with any specific safety concern under the proposed conditions of clinical use. As faster bone regeneration in a dental defect would ensure that patients can receive an implant at an earlier stage, it has the added benefit that accelerated healing will be accompanied by more rapid resumption of other daily and leisure activities, with the obvious benefits for quality of life.
It is important to note that all control measures for the clinical trial batch have been validated. The tests are in place and have been verified and found to be effective for product release.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

• Males and females, aged >=18 years.
• Patient has signed informed consent.
• Patients with a ruinous dentition (including the canines) in the lower jaw in need of extractions of all teeth of the mandible.
• Patients in need of a total dental prosthesis in the lower jaw.
• Patients that want an implant-based denture in the lower jaw.
• Bone width of at least 7mm
• Bone height beneath the root-point of the canines at least 10mm

Exclusion criteria

• Absence of the lower canines
• Concomitant Medication: prescription or nonprescription drugs affecting bone-metabolism, including corticosteroids, gonadotropins, sex steroids (not: contraceptive medication), bisphosphonates, denosumab, parathyroid hormone and calcitonin.
• History of radiotherapy in the head/neck region
• Poor oral hygiene
• Women who are pregnant or breastfeeding
• Compromised immune system (e.g. uncontrolled diabetis) or unstable bleeding disorder.
• Patients with ASA classification of III or worse
• Local infection at the site of implantation
• History of previous ridge augmentation/preservation at the site of interest
• History of oral cancer or radiation of the oral cavity.
• Current malignancy
• Unresolved oral pathologies
• Patient does not give permission for implantation of porcine membrane.
• Highly atrophic mandible (Cawood classification V or higher)
• Known allergy to collagen.
• Heavy smoking (> 20 cigarettes/day).

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	31-08-2021
Enrollment:	16

Type: Actual

Medical products/devices used

Generic name: OsteoActivator-P

Registration: No

Ethics review

Approved WMO Date: 07-05-2021

Application type: First submission

Review commission: METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 29312
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL76937.068.21
Other	NL9346

Study results

Date completed: 31-01-2024

Summary results

Trial ended prematurely