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IMPROVED OSSEOINTTEGRATION OF METALLIC IMPLANTS BY THE USE OF BONE MORPHOGENETIC PROTEIN-3 (BMP-3)

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INTRODUCTION

The long-term stability of a non-cemented implant depends on intraoperatively achieved primary stability as well as on secondary stability resulting from ingrowing bone tissue. In addition, long-term stability also depends on strain to the implant. Surface increase by means of structuring as well as coating of the implant with biologically inert and bioactive porous material are supposed to shorten the time interval until secondary fixation of the implant occurs. In regard to long-term stability the development of implants which foster their own osseointegration by way of releasing osteoinductive proteins is of great importance. This trial studied the osseointegration of metal test implants of various surface qualities in spongy bone matter of 12 German shepherd dogs with and without bone morphogenetic protein 3 (BMP-3) coating. The main objective of our study was to determine whether additional coating of implants with BMP-3 would improve the osseous solidification of the implants.
MATERIALS AND METHODS

A cylindrical test object made of titanium-aluminum-vanadium alloy (Ti-Al-V) was chosen as an implant. The implant with a total length of 12 millimeters (mm) consisted of a collar with a diameter of 7.3 mm ± 50 μm and a length of 2 mm sitting on top of a shaft of 5 mm length and 5 mm diameter ending in a pointed cone of 5mm depth.

Half of the 48 implants were laminated with a hydroxyapatite surface, the other half with plasmapore. 190 μg of highly purified BMP-3 precipitate isolated from porcine bone was available for the coating of each of 24 cylindrical test implants (12 with hydroxyapatite and 12 with plasmapore surface). The remaining 24 test implants with the same surface makeup served as negative control groups.

The test implants were then implanted into the medial and lateral femoral condyle of both legs of 12 adult German shepherd dogs utilizing pressfit anchoring. Implantation sites were randomly assigned for the four versions of implants available. In order to embed the test implants, holes were drilled into the condyles and a bone cylinder extracted. The drilling holes were executed in such a fashion that after implantation of the cylindrical test implant a gap of 1.1 mm remained surrounding the implant.

The implantation was not followed by any period of restriction of activity or non-weight bearing restraint. All animals were allowed normal weight bearing activity right after surgery.

All animals were marked in vivo using fluorochrome stains in order to monitor the distribution of new bone formation and apposition to the implant during the time of the trial.

Explantation of the test implants was performed after bone consolidation on the 42nd postoperative day.

RESULTS

42 days after surgery, all implants presented with a similar radiographic appearance, independent of the surface make up. No morphological differences with regard to the various implant groups were visible on radiological examination and all implants were well integrated.

The osseous integration of the extracted test implants was biomechanically assessed by the amount of force necessary to extract the implant. This reaffirmed the firm bony integration of the implant. BMP-3 coating increased the recorded maximal extraction force but
also the shear force to the bone-implant-interface in the hydroxyapatite-plated implants by about 70% compared to the non-BMP-3 coated control implants. There were only minor differences with regard to maximal extraction force as well as shear force to the interface (10%) between BMP-3 coated and non-coated plasmapore implants. The Wilcoxon signed-rank test was utilized to test for statistical differences (p < 0.05). The BMP-3 coated HA-test implants exhibited a significantly better osseous integration when pull-out force data were compared. Between the BMP-3 coated and control plasmapore implants no significant differences could be verified.

There was no significant difference in regard to osseous integration between the two different laminations (hydroxyapatite versus plasmapore lamination).

Serial slices of 16 compounds were prepared perpendicular to the central axis of the implant and analyzed taking into account their topographical and anatomical position at a wave length of 240 to 270 nanometers utilizing a light microscope. The aforementioned radiographic results were confirmed by fluorescence microscopy. All BMP-3 coated HA-test implants exhibited a connective tissue-free bony integration with the formation of a tangential bone ring surrounding the whole implant. As far as bone density was concerned, adding BMP-3 to the test implants led to an increase in the formation of new bone tissue and to a widening of the implant-bone contact zone. In the test implants with HA lamination without BMP-3 coating the bone density in the gap around the implants was comparatively lower. The bone bed was similar to the BMP-coated test implants – partially consolidated comprising lamellar-concentric bone structures and partially comprising cancellous bone. All plasmapore laminated implants exhibited new bone formation in the gap around the implant. This bone formation was, however, less well advanced compared to the HA laminated implants. Around HA-test implants new bone formation took the shape of a circumferential tangential ring whereas plasmapore laminated implants were surrounded by a purely trabecular bone support structure. BMP-3 coating had a less positive effect on bone formation in implants laminated with plasmapore than in HA implants. All plasmapore laminated implants without BMP-3 coating, regardless of sufficient bony integration, exhibited some degree of connective tissue membrane coverage around the surface circumference of the implants.

In order to assess the direct bone growth onto the implant, digitalized image analysis was performed. That enabled us to calculate the
percentile of all implant areas of bone ongrowth in relation to the total surface of the implant. The extent of direct bone implant contact surface in the study population was between 4 and 49%. In both implant groups with BMP-coating a definite synergetic effect was verifiable. The bone ongrowth surface area in the HA-coated implants was 2 to 3 times more extensive than in the plasmapore-coated implants. In comparison to the control groups BMP-3 coating led to a 58% increase of the implant bone ongrowth surface and to a 130% increase in plasmapore test implants. It was remarkable that there was more extensive direct bone ongrowth to the implants even in non-BMP-coated HA laminated implants (negative control) when compared to BMP-3-coated plasmapore laminated implants. The differences between the BMP-3 coated and control group implants were tested for significance using the Wilcoxon test for small groups. With regard to osseous integration (implant bone ongrowth), a significant increase due to BMP coating was recorded in the comparison of the two groups of hydroxyapatite laminated implants 42 days after implantation (p < 0.0625). In plasmapore-laminated implants, a significant supportive effect of BMP-3 coating with regard to osseous integration was not verifiable because the test groups were too small.

CONCLUSIONS

Primary stability of the implant was achieved by anchoring the implant collar securely regardless of the 1.1 mm gap surrounding the implant which simulated the usual clinical situation. This allowed for a reproducible examination of the bone healing process in the gap around the implants under the influence of BMP-3. For this study, a titanium-BMP-composite in the bone bed of a dog was validated to be osteostimulative or osteoinductive when the amount and quality of the new bone formed in the gap around the implant within the given observation period was more extensive and of better quality then bone formed when osteoreparation had taken place without induction or stimulation.

All HA laminated implants with or without BMP coating presented with adjunctive osteogenesis free of connective tissue. In the titanium-plasmapore laminated test implants with or without BMP coating, however, interposing thin sections of connective tissue were found.
Our results confirm earlier findings of Soballe et al. (1) who compared hydroxyapatite laminated and titanium plated implants in a similar animal model based study. 4 weeks after implantation, titanium implants exhibited comparatively less new bone formation in the gap surrounding the implants.

The histomorphometric data for the hydroxyapatite surface were confirmed by tensile strength testing. The recorded shear forces at the bone-implant interface of BMP-3 coated implants exceeded those of the control group by 70%. In plasmapore implants, on the other hand, we recorded only slightly higher shear forces as compared to the control group. This is caused by the significantly higher roughness of the plasmapore surface (Ra 27.8 µm) as opposed to hydroxyapatite surfaces (Ra 7.9 µm) which leads to a stronger interlink of trabecular bone with the implant surface as well as a unexpectedly high shear force at the interface. BMP-promoted osseointegration could therefore not be established for the plasmapore surface.

An increase in the surface of the implant by way of three-dimensional interconnected pores promotes the osteogenic capacity of the applied growth factor and leads to a well ordered release of BMP-3 from the carrier. The hydroxyapatite surface is superior to the titanium-plasmapore surface in regard to the observed parameters because of its pronounced bioactivity and its osteoconductive characteristics.

REFERENCE