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Critical Appraisal»

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Critical Appraisal

The effect of matrix bound parathyroid hormone on bone regeneration

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1. Introduction

Crestal and basal implants are endosseous aids to create osseointegrated point

References:

Jung, R. E., Cochran, D. L., et al. (2007). „The effect of matrix bound parathyroid hormone on bone regeneration." Clin Oral Implants Res 18(3): 319-25.

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ARTICLE SUMMARY

Authors' Summary:
Arginine-glycerine-aspartic acid (RGD) modified polyethylene glycol-based matrix (PEG) hydrogel containing parathyroid hormone (PTH1-34) is an effective matrix system to obtain bone regeneration.

Study Objectives:

To test the hypothesis that an RGD-modified PEG containing covalently bound peptides of the PTH1-34 enhances bone regeneration to a degree similar to autogenous bone.

Design: Animal model, randomized treatment modalities.

Sampling: Six American foxhounds (age not reported). Forty-eight cylindrical titanium implants placed in the mandible between the first premolar and the second molar. In the total of six animals, four implants were placed 5 months after tooth extraction in one side of the mandible and four implants after 7 months in the other side of the mandible

Implant design:

• All implants were cylindrical with a large sand-blasted and acid-etched (SLA) surface (Institut Straumann AG, Basel, Switzerland).

• Exhibited a screw design in the apical half only.

• Outer diameter without the threads measured 2.8 mm and implant length measured 8 mm.

Interventions:

Two surgical interventions were performed at 5 months and 7 months after tooth extraction. A total of 48 implants were placed into

the center of the surgically created defect obtaining primary stability. This resulted in a circumferential bone defect with a circular gap of 1.5 mm. The 4 implants inserted per time point in each dog were randomly allocated to four treatment modalities:

- PEG matrix containing 20 µg/ml of cys-PTH1-34 and 350 µg/ml cys-RGD peptide (matrix-PTH)
- PEG alone
- Autogenous bone (positive control)
- Empty defect (negative control)

The autogenous bone was harvested during the drilling process from each of the four defects and was used to augment the site determined for autogenous bone. Primary wound closure was achieved with interrupted sutures. Animals were sacrificed 4 weeks after last surgery.

Outcome Measures:

- Histomorphometric analysis was performed 4 and 12 weeks after implantation.
- The area fraction of newly formed bone was determined within the former defect and the degree of bone-to-implant contact (BIC) was evaluated both in the defect region and in the apical region of the implant.

Results:

- All 48 implants were osseointegrated after 4 and 12 weeks of healing.
- No biologically significant abnormality was observed in association with any treatment procedures.
- After both 4 and 12 weeks the matrix-PTH group and autogenous bone group demonstrated a higher area fraction of newly formed bone within the former defects, Table.
- Statistically significant differences in area fraction of newly formed bone within the former defect were observed for the matrix-PTH group compared with PEG alone (4 weeks, $p<0.01$; 12 weeks $p<0.05$) or empty controls (4 weeks, $p<0.05$; 12 weeks $p<0.05$).
- No difference could be detected compared to the autogenous bone group.
- The PEG alone showed no significant difference compared with empty defects.
- Differences between groups were larger after 4 compared to 12 weeks of healing.
- The area fraction of newly formed bone had significantly increased from 4 to 12 weeks for all treatment groups
- The empty control showed the least bone area at both time points.
- No significant difference was observed between the 4 treatment groups at 4 or 12 weeks with respect to bone-to-implant-contact.

Table. Average area fractions (%) of newly formed bone at 4 and 12 weeks

Timing	Empty control	Autogenous bone	PEG alone	Matrix-PTH
	Mean (%) ± SD	Mean (%) (%) ± SD	Mean (%) ± SD	Mean (%) ± SD
4 weeks	28.9 ± 1.5	43.9 ± 4.5	26.6 ± 4.1	41.7 ± 1.8
12 weeks	38.7 ± 1.9	50.5 ± 3.4	39.3 ± 5.7	49.4 ± 7.0

REVIEWER'S EVALUATION

Methodological Principle	
Randomized design	YES
Blinded surgeon	NO
Independent or blind assessment	NO
Adequate sample size	NO†
Appropriate analysis	YES
Controlling for possible confounding	YES*
Appropriate measures	
Histological analysis	NO
Histomorphometric analysis	YES
Biomechanical analysis	NO

*Matched design – same animal served as control and implants were randomly allocated.

†Sample size was large enough to demonstrate statistical significance at each follow-up, however, did not account for the multiple surgeries that inherently have an impact on bone remodeling.

1. What were the study's methodological strengths?

- Subjects served as their own control.
- Implants were randomly allocated to jaws.
- Appropriate analyses were performed on the measures selected

2. What were the study's methodological limitations?

It is unclear if the surgeon who inserted the implants was blind to the implant type. Surgical insertion may influence outcomes.

• It is unclear who assessed the outcomes in these experiments and if they were blinded to the procedure. An independent assessor blind to the technique of preparation would ensure that known or unknown evaluation bias did not occur.

• No biomechanical testing was performed. Biomechanical testing should always be included in this type of an assessment as observed osseointegration may not necessarily translate to implant stability.

• Animal studies are limited in terms of their generalizeability to humans. They are critical in the early phase of studying a new intervention; however, healing properties differ, and more importantly, a safety profile of Matrix-PTH cannot be established from this study.

• The investigators focused only on the bone-to-implant side of the experiment and did not report on the augmentation-to-bone-side of the experiment. Figures 4 and 5 show dramatic osteolysis in the region of the "old bone". This may indicate that although the bone to implant contact may be increased, the overall load transmission capacity of the newly built bone is reduced. On the other hand, it may indicate that the integrity of the whole mandible of the dog was endangered by this experiment.

• Based on this observation, we can not be sure that the contents of the Matrix PTH-defects did not influence the other defects in the same half of the jaw. As bone is known to have 0-1 properties (i.e. self trabeculating properties), strong remodeling in one area will naturally influence regeneration in other areas.

• Furthermore, we should consider that performing an operation 5 months post tooth extraction and another operation at 7 months post tooth extraction stimulates a constant state of strong bone remodeling. This remodeling even reaches non-operated areas. (Atkinson PJ, Woodhead C, Powell K (1974): The influence of remodeling on mandibular bone structure. Oral Implantology, 4(3):263–293):

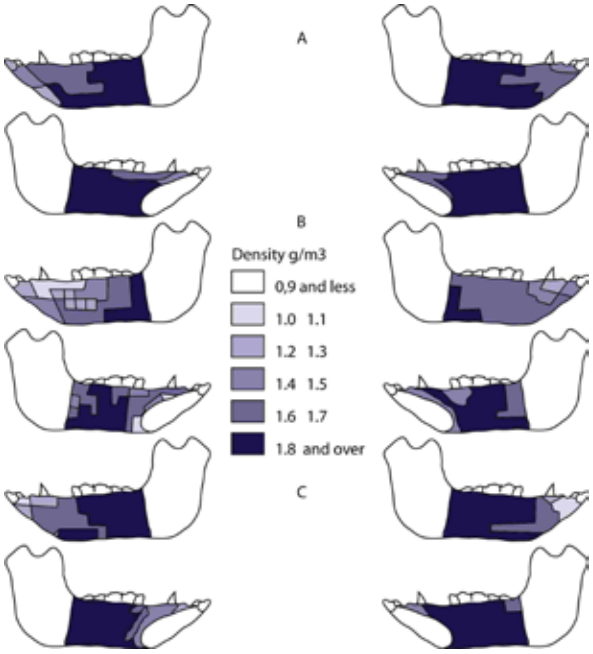

Fig. From Atkinson et al, 1977: Bone remodeling and change in density after implant placement in one area of the pigs mandible. Distribution of mineralization at A (postop), B (3 months), C 12 months). Note that surgery in one single location will influence the bone in all areas of the mandible.

From this we can conclude that implant sites which have received implants at 5 and 7 months after extraction are not comparable. First, the sites still suffer from the extraction procedure and cannot be considered as "healed" at this stage. Second, the sites operated at 7 months are structurally influenced by the contralateral sites which were operated at 5 month post extraction.

Based on the aforementioned physiology, the sample size becomes too small for all assessments as the bone sites are not enough for two experiments.

3. Was the preparation of the implant sites appropriate and relevant to the clinical setting?

This type of bone preparation is never used in human implantology. Defects of this kind may be present when peri-implantitis creates crater-like defects; however, these defects have a different shape and they are corticalized. There is no conceivable clinical setting that can resemble this experiment.

4. Were all important assessments performed?

It would have been necessary to determine bone mineral density in all regions of the mandible in order to evaluate the situation of the bone. Cylinders of bone could have been taken out of the mandible during surgery to make this determination.

mandible during surgery to make this determination

5. Are there alternative explanations for the findings observed in this study?

As explained, the sample size is too small to give realistic statistical results. Therefore all "results" should be handled with caution.

6. How might the findings of this animal study be applied to patient care?

Since the defects created here never occur in this way in humans and implants are never inserted into humans under the conditions of this experiment, we can not transfer any results to the situations in humans.

Figures 4 and 5 demonstrate that extreme skepticism is justified, when Matrix PTH is applied to humans. In both figures, large defects inside the old bone are visible. While the researchers may have been optimistic about the overgrowing of bone over the top of the implant (a phenomenon which usually is created by function alone and not so much by the augmentation material unless it is placed there), they appeared to not pay attention to the left side of the histological picture which shows clear warning signals. The group reports that the bone in the apical region of the implant was unaltered in all implants. We can trust this report because we know basal osseointegrated implants show reliable and solid integration.