Improved and more predictable vertical bone augmentation using synthetic dicalcium phosphate block grafts containing a novel bisphosphonate-EP4a conjugate drug (C3)

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BACKGROUND & OBJECTIVES

- The long-term success of dental implants is dependent upon the degree of osseointegration in sufficient and healthy bone. [1]
- Synthetic alternatives to replace autografts for alveolar ridge augmentation are actively sought to overcome autograft limitations such as extended operative time, the risk of infection and most importantly, limited quantities of autologous bone available. [2]
- It has been shown that dicalcium phosphate (DCP) biomaterials, brushite and monetite are biocompatible, osteoconductive and resorb faster and more than other materials such as hydroxyapatite (HA). [3]
- Brushite is stronger than monetite but resorbs less and converts to slowly resorbing hydroxyapatite after implantation., Whereas, Monetite resorbs faster and does not convert to HA resulting in greater bone infiltration.[4]
- We have developed DCP grafts (monetite) that incorporate in their matrix a novel bone anabolic conjugate (C3) of an inactive bisphosphonate (bone targeting agent), an enzymatically hydrolyzable linker and a potent osteoblast activating agent (a potent and selective agonist for the EP4 prostaglandin receptor subtype)
- The primary objective of this research was to investigate whether the EP4a released from the conjugate drug C3 within the matrix of the monetite grafts has the potential to achieve rapid, enhanced and clinically significant bone regeneration in the vertical dimensionin in a preclinical rabbit calvarial model.

METHODOLOGY

FABRICATION OF DCP GRAFTS WITH & WITHOUT C3 DRUG

*Brushite block grafts (9.5 mm x 4 mm) with and without C3 drug (0.1% concentration) in the matrix were fabricated using Beta-tricalcium phosphate (β TCP), Monocalcium phosphate monohydrate (MCPM) and deionized water (with and without C3 drug)

*The pre-set brushite block grafts were converted to monetite by autoclaving treatment. It was confirmed that this did not affect the C3 drug adversely

*The Monetite grafts were characterized for porosity (19 %), density (2.87 g/cm^3) and mechanical strength. (6.5 MPa compressive strength)

IMPLANTATION & ANALYSIS OF THE GRAFTS

*The monetite grafts were implanted in pairs on 6 White New Zealand rabbit calvaria for 12 weeks stabilized with titanium osteosynthesis screws (*n*=6 for each group)

*After 12 weeks, the animals were sacrificed and the grafts with calvarial bone blocks retrieved and analyzed for bone augmentation and graft resorption using electron microscopy and histomorphometry . Mann-Whitney test was used to evaluate head-to-head differences between the implanted grafts and statistical significance value was set at a P < 0.05.

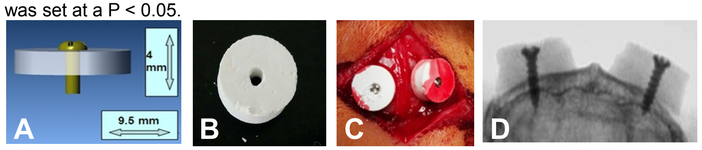

Figure 1: (A) Schematic representation of the graft dimensions. (B) Monetite graft disc with drill hole. (C) Implantation of monetite grafts stabilized with titanium screws. (D) Post implantation X-Ray of grafts

RESULTS

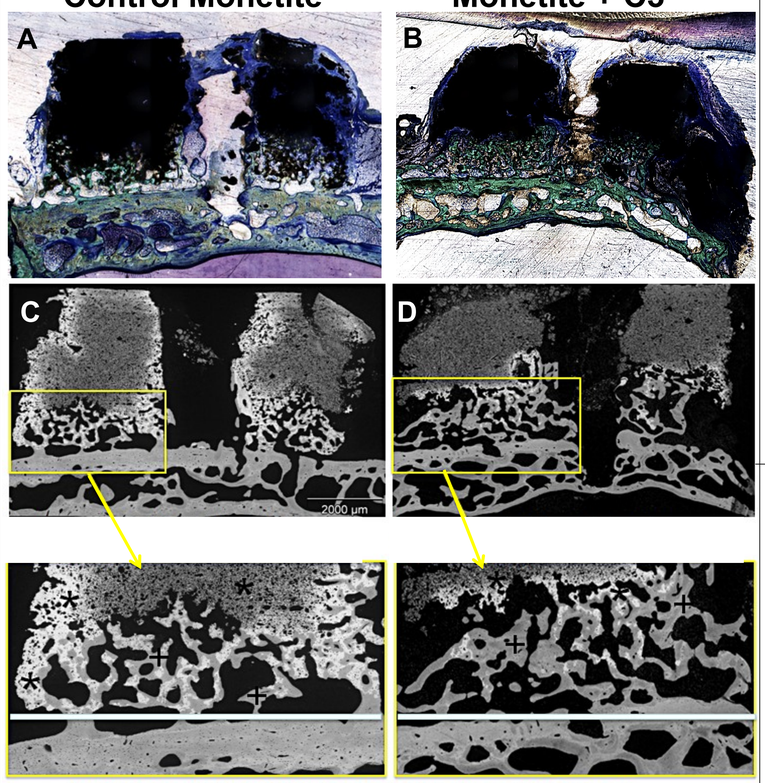

Figure 2: (A & B) Histological micrographs of control monetite and C3 containing monetite grafts. (C) The B-SEM micrographs of control monetite grafts showed more remaining monetite material in the augmented area and less bone tissue. (D) The B-SEM micrographs of the C3 containing monetite grafts showed less remaining monetite material in the augmented area and more bone tissue infiltration.

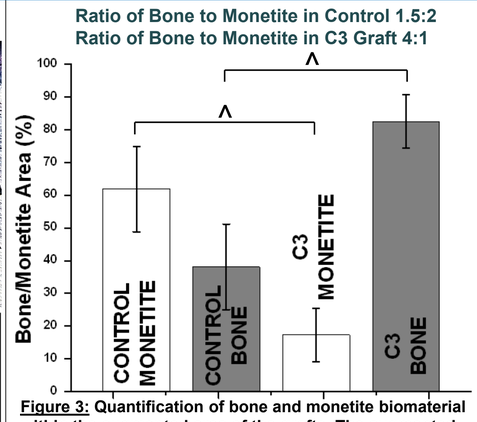

Figure 3: Quantification of bone and monetite biomaterial within the augmented area of the grafts. The augmented area of C3 containing grafts had greater bone tissue and less monetite biomaterial (The statistical significance set at a value of P < 0.05 and denoted by ^)

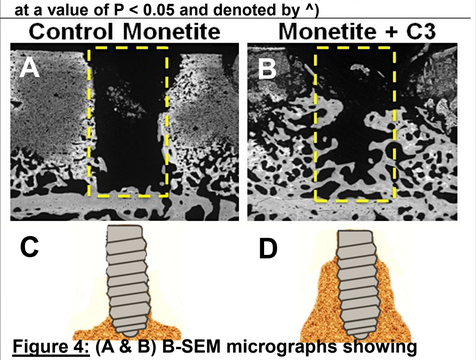

Figure 4: (A & B) B-SEM micrographs showing greater bone formation via osteoconduction along the surface where the titanium screw was present. (C & D) Bone growth stimulation along the implant surface would be expected to promote osseointegration and stability

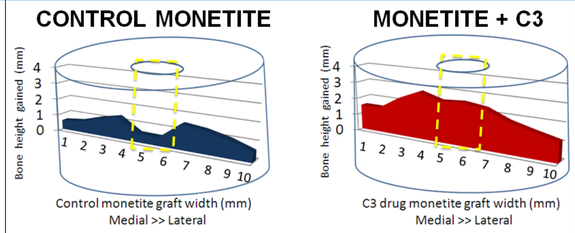

Figure 5: Mapping of bone height gained along mediolateral axis of monetite grafts. The grafts containing C3 had greater bone gain along the graft length

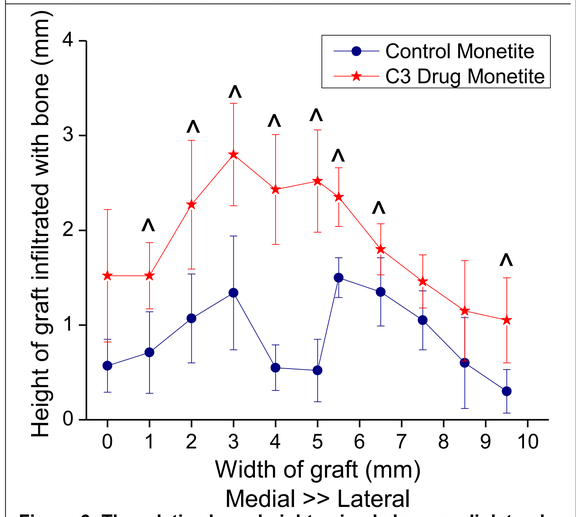

Figure 6: The relative bone height gained along mediolateral axis of monetite grafts with and without C3. The monetite grafts containing the C3 conjugate in their cement matrix had a significantly greater height gain in the vertical dimension in comparison to the grafts without C3. (The statistical significance set at a value of P < 0.05 denoted by ^)

CONCLUSIONS & CLINICAL RELEVANCE

*The C3 containing Monetite grafts integrated well onto the bone surface with mature bone extending through the graft area, while the C3 lacking grafts showed absence of mature bone and surface integration. In addition, the C3 containing monetite grafts demonstrate bone growth vertically up along the titanium screw surfaces which would be clinically very relevant in terms of implant stability and osseointegration.

* Some potential advantages of using these monetite/C3 graft materials are: Faster bone healing; Better quality bone (improved implant stabilization); Faster Implant integration; Predictable regeneration of bone around teeth and implants and no need for donor site. Here we present results from a novel anabolic bone graft formulation and confirm its efficacy in an implantation model which shows promise to ultimately benefit millions of patients undergoing bone augmentation for dental implant therapy.

REFERENCES

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2. Sheikh *et al.* Materials, 2015
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FUNDED BY:* *CIHR POP Grant.
American Academy of Implant Dentistry Foundation (AAIDF).
Alpha Omega Foundation of Canada.