Effects of different doped hydroxyapatite-based materials on healing of critical size calvaria bone defects in rats

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INTRODUCTION: Nanosized synthetic hydroxyapatite (HAp), closely resembling biological apatite found in human bones and teeth, is extensively studied for its potential in hard tissue repair. Ion-doping of HAp with therapeutic ions is emerging as a promising strategy to mimic biological apatite, promoting specific biological responses such as osteogenesis, angiogenesis, increased cell proliferation, and antimicrobial activity [1]. The aim of our study was to explore and compare the effects of Sr,Cu co-doped α tricalcium phosphate (αTCP) with/without Mg doped HAP on healing of critical size rat calvaria defects *in vivo*.

MATERIALS AND METHODS: Nanosized HAp powders, both single-ion doped with 5 mol.% Mg and co-doped with 3 mol.% Sr and 0.4 mol.% Cu ions , were synthesized using a modified hydrothermal method and α-TCP powder was obtained by calcination of the doped HAp at 1500°C for 2 h [1]. Six male Wistar Albino rats, 8 weeks old, were used to surgically induce two 5 mm bone defects on calvaria [2]. The defects were augmented with either Sr,Cu αTCP with/without Mg HAp material or with "gold standard" material, Bio-OSS (Geistlich Pharma, Wolhusen, Switzerland). Animals were sacrificed 8 weeks after augmentation. Collected tissues were further analyzed using CBCT, histology and qRT-PCR. Collected data were analyzed statistically.

RESULTS AND DISCUSSION: Results of CBCT analysis presented high defect closure using Bio-OSS and Sr,Cu αTCP, and median level of closure when using Sr,Cu αTCP/Mg HAp (p<0.05). This difference could be due to high levels of endothelial cell stimulation by magnesium ions [3] contributing to higher closure by fibrous tissue as presented in our histological analysis. However, using both Sr,Cu αTCP or Sr,Cu αTCP/Mg HAp resulted in stimulating mineralized tissue deposition. In our qRT-PCR analysis, Sr,Cu αTCP and Bio-OSS similarly (p>0.05) increased the expression of proinflammatory cytokine TNF-α, unlike using Sr,Cu αTCP/Mg HAp which showed lower levels (p<0.05). This could again be appointed to the aforementioned effect of magnesium ions [4]. Interestingly, both Sr,Cu αTCP and Sr,Cu αTCP/Mg HAp presented higher expression of TGFβ, a growth factor connected with better bone regeneration, compared to Bio-OSS. Additionally, all tested materials presented similarly high expression of ALP, known marker of osteogenic differentiation. However, Bio-OSS presented significantly higher RANKL/OPG ratio, a marker indicating osteoclastic activity, compared to Sr,Cu αTCP, while Sr,Cu αTCP/Mg HAp showed the lowest values.

CONCLUSIONS: This study demonstrates that Sr,Cu αTCP and Sr,Cu αTCP/Mg HAp exhibit promising bone healing outcomes of critical size calvaria defects, comparable to that of Bio-OSS.

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