• A MAGNESIUM INJECTABLE FORMULATION ADHERES BONE TO BONE AND TENDON TO BONE

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HYPOTHESIS: A biodegradable monopotassium phosphate (54%), magnesium oxide (33%), tricalcium phosphate (9%), C/12H/22O/11 (4%) injectable formulation will adhere bone and tendon to bone.

INTRODUCTION: Injectable biodegradable fillers and cements can provide an osteoconductive matrix to fill bone defects during the bone repair process. Depending on the characteristics of the material, potential exists for structural support and delivery of osteoinductive and cell based therapies.[1] Degrading magnesium alloys as implants for osteosynthesis have demonstrated an osteoproliferative effect in vivo and enhanced mineralized bone area compared to degradable polymers.[2] Magnesium [Mg]-based products offer other potential advantages, such as a resorption profile more compatible with normal bone healing[2], low toxicity, and controllable radiodensity. Current formulations of injectable calcium [Ca] phosphate compounds are biocompatible, but most show prolonged presence even in normal highly vascular trabecular bone[3] and may be associated with lethal embolization[4].

To date, adhesive properties have not been reported or claimed for experimental or commercial bone fillers or cements. The specific goal of this study was to determine if an injectable Mg-based formulation had adhesive properties for bone to bone and tendon to bone using clinically relevant models and comparison to a Ca-based commercial product. Biomechanical studies were performed using a canine cadaver model of anterior cruciate ligament repair and femur fracture. Tissue adhesion was quantified with mechanical pull-out and three-point bending studies.

METHODS: Sixteen knee joints with femurs and Achilles tendons from 8 mid-sized dogs were harvested and three tissue specimens for testing were prepared.

ACL Model: *A) Bone to Bone*. Patellar bone-tendon grafts were formed and the patella bone press-fit into a 7mm diameter bone tunnel drilled in the femur at the ACL footprint to mimic human ACL reconstruction. (Fig 1-Femur) *B) Tendon to Bone*. Achilles tendon grafts were placed through a 7mm diameter tibial bone tunnel initiated at the ACL footprint and exiting the lateral tibial cortex to mimic human ACL reconstruction. (Fig 2-Tibia) Implants were not used to augment these repairs. The tendon ends served as the anchor for pull out mechanical testing. Treatment groups were: 1) Press-fit (Control; n=16); 2) Ca-based injectable formulation (n=8) [Negative paste control] [Norian Skeletal Repair System- Synthes, Paoli, PA]; 3) Mg-based injectable formulation [Bone Solutions, Inc. Dallas,TX]. Limbs were paired for groups 2 and 3. Product was prepared and injected into the bone defects surrounding the bone or tendon grafts in the bone tunnels and allowed to cure overnight. Grafts were mechanically tested in tension for peak load to failure at 1mm/sec.

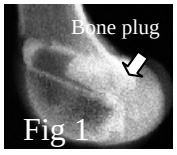

Fig 1

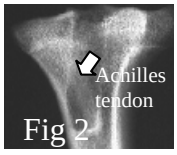

Fig 2

Fracture Model: A 1cm long oblique osteotomy was made in the midshaft of the femur diaphysis and four materials tested to secure the fracture in reduction: 1) Blood clot [freshly clotted equine blood]; 2) cyanoacrylate [Ross Super Glue Gel- Ross Products, Columbus, OH); 3) Ca-based injectable formulation [Norian Skeletal Repair System- Synthes, Paoli, PA]; 4) Mg-based injectable formulation [Bone Solutions, Inc. Dallas, TX]. Additionally, four intact femurs were tested to failure. Groups 3 and 4 were tested in paired limbs. Groups 1 and 2 were tested in paired limbs; one half before and one half after application of the paste products in groups 3 and 4. First tested products were readily removed by scraping. Injectable pastes and cyanoacrylate were applied liberally to the fractured bone ends, held together for 15minutes until hardened, and allowed to cure overnight. (Fig 3) Femurs were tested in 3-point bending under displacement control at 0.1mm/sec for peak load to failure. Stiffness and stress to failure were calculated from the slope of the linear portion of the load deformation curve and after estimation of bone area at the fracture with calipers. Fractures which fell apart before testing were recorded as 0 N to failure.


Fig 3

Data in the ACL model were analyzed with the paired Student's t-test for calcium vs magnesium formulations and for press fit vs formulation. Data in the fracture model were analyzed with a 1-factor ANOVA for treatment group. Significance was set a $p<0.05$.

RESULTS: In the ACL model, both the Ca-based formulation and the Mg-based formulation had significantly greater pull out force than press-fit (friction) within the tunnel for both patellar bone and Achilles tendon ($p<0.003$). The Mg-based formulation had the greatest adhesive properties, significantly greater than the Ca-based formulation for both bone (2.5-fold;$p<0.003$) and tendon (3.3-fold;$p<0.009$). **(Table 1)**

Table 1. ACL Model – Peak mean (+/- SEM) tensile load (N) to failure. [Different letter superscripts are different; $p<0.003$)

Groups	Press-fit	Ca-based Formulation (Norian™)	Mg-based Formulation (BoneSolutions)
Bone-Bone	41.6 +/- 16.8[a]	427.7 +/103.9[b]	1025.6 +/-118.2[c]
Tendon-Bone	12.9 +/- 0.03[a]	101.6 +/- 23.1[b]	338.2 +/-69.9[c]

In the fracture model, blood clot and Ca-based formulation had no adhesive properties (0 N load to failure) in all specimens. Blood clot was unable to hold the two ends of the femur in apposition. The Ca-based product held the femur ends in apposition, but separation occurred prior to testing. Mg-based formulation and cyanoacrylate failed at significantly greater loads than Ca-based formulation or blood clot ($p<0.00001$) and cyanoacrylate failed at significantly greater loads than the Mg-based formulation (127 N vs 37.7 N, respectively; $p<0.01$). Intact femurs failed at much greater loads. Bone adhesives achieved < 10% of original bone strength. **(Table 2)**

Table 2. Mean (+/- SEM) biomechanical properties to failure in femur osteotomies repaired with potential bone adhesives. [Within parameter, different symbols are different $p<0.01$]

Groups	Peak Load (N)	Peak Stress (N/mm^2)	Stiffness (N/mm)
Blood Clot	0±0*	0±0*	0±0*
Ca-based Formulation (Norian™)	0±0*	0±0*	0±0*
Mg-based Formulation (BoneSolutions)	37.7±8.9**	0.09±0.01**	148.7±35.4**
Cyanoacrylate	127.0±27.9§	0.3±0.03§	783±94.1§
Intact Femur	1455.8±127†	4.18±0.17†	666.8±65.3†

DISCUSSION: In bone and tendon pullout from a bone tunnel, paste formulations provided some adhesion due to cement properties (ie hardened filler). However, the Mg-based formulation had additional, significant, and substantial adhesive properties of over 1000 N in bone that should exceed forces put on the construct in vivo. In femur fracture reconstruction, the magnesium formulation provided bone adhesion, although less than the positive control glue. Cyanoacrylate is not biodegradable and impairs bone healing.

CONCLUSION: A biodegradable monopotassium phosphate and magnesium oxide injectable formulation adhered bone and tendon within bone tunnels sufficiently to significantly augment, or potentially be used independently, in ACL reconstructions. Adhesion of bone ends may be sufficient to contain fracture fragments in comminuted fracture repair and may be useful if osteoconduction and biodegradation profiles complement fracture healing as anticipated.

REFERENCES:1)Seeherman *et al*.(2003) JBJS **85A**:96; 2)Witte *et al*. (2004) Trans ORS:256; 3) Apelt *et al*. (2004) Biomaterials **25**:1439; 4) Bernards *et al*. (2004) Trans ORS:254;

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