

## Evaluation of Setting Times for Combinations of Bone Void Fillers mixed with Antibiotics

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**Introduction:** Treatments for osteomyelitis include intravenous injection of drugs and local implantation of antibiotics containing polymethylmethacrylate (PMMA) beads. Disadvantages of these treatments include recurring infection, and requirement for a second operation to remove the PMMA beads<sup>1</sup>. Resorbable bone void fillers, such as calcium sulfate ( $\text{CaSO}_4$ ), with antibiotics for local drug delivery may provide a clinically useful alternative by delivering high levels of antibiotics to local tissue and mitigating risk of second surgery morbidity, given an appropriate antibiotic release profile within a relevant period of time. Additionally, self-setting  $\text{CaSO}_4$ /antibiotic composites must possess handling and setting time characteristics that are practical for on-site use during surgery. Minocycline (M) and rifampin (R) are a patented antibiotic combination shown to be clinically effective against common orthopedic infections and useful for mixing with  $\text{CaSO}_4$ <sup>2</sup>. Setting time and release rates of M and R may differ between hemihydrate (Hemi) and dihydrate (Di) powder forms of  $\text{CaSO}_4$ . The objective of this study is to determine effects of M and R on setting times of  $\text{CaSO}_4$  Hemi and Di mixtures of various ratios (Hemi:Di) in order to find the mixture with the most clinically useful working time.

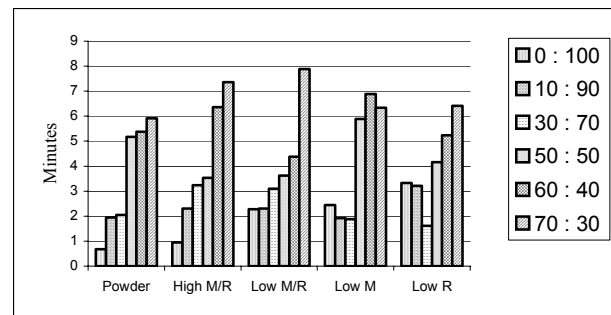
**Methods:** Mixtures of BonePlast™ (Biomet Irvine, Inc., Irvine, CA) –  $\text{CaSO}_4$  Hemi, and Calcigen S™ (Biomet Orthopedics Inc., Warsaw, IN) –  $\text{CaSO}_4$  Di in different ratios were manually combined with M and/or R and mixed with potassium citrate/sodium phosphate solution. Components were stirred together for 2 minutes to produce a homogenous paste, and allowed to set to form composite beads (6-mm diameter). For each ratio of Hemi:Di (10 g total): Group 1: Control (no drugs) Group 2:  $\text{CaSO}_4$  + M/R (62.5mg M, 62.5mg R), Group 3:  $\text{CaSO}_4$  + M/R (12.5mg M, 12.5mg R), Group 4:  $\text{CaSO}_4$  + M (12.5mg M) and Group 5:  $\text{CaSO}_4$  + R (12.5mg R). After mixing, setting time was recorded using a timer (Cole Parmer, Fischer Scientific). Setting completion was checked by pressing pellets with a blunt metal instrument. Pellets were considered hardened if no impression could be made.

**Results:** Setting times for Groups 1 thru 5 are presented in Figure 1. The 60:40 mixture ratio showed the most clinically feasible setting time ranging from 4.38 minutes to 6.88 minutes. Setting times increased as ratios of Hemi increased and Di decreased. Interestingly, high and low dosages of M and R together increased setting times in all groups except for the 50:50 mix. Compared to controls, R alone increased the setting time for low concentrations of Hemi, but did not affect the setting time in the 60:40 mix. M increased the setting time in all groups.

**Discussion:** M and R in combination have been in clinical use for almost four decades and have shown efficacy *in vivo* and *in vitro* for preventing colonization and infection against gram-positive and gram-negative bacteria<sup>2, 3</sup>. This patented combination has also been

shown to be more effective than other antibiotic combinations against staphylococci, which can be extremely useful in treating osteomyelitis. M and R are not antagonistic in combination, though they can be occasionally synergistic<sup>4</sup>. The combination is not known to exhibit immunogenicity or allergic reactions in patients. These considerations made M and R good candidates for evaluation with  $\text{CaSO}_4$  bone void filler.

The unexpected result of this study was that M and R together in low concentration greatly decreased the setting times in some of  $\text{CaSO}_4$  Hemi ratios. Likewise, the combination increased setting times at high concentration of M and R. However, increasing the ratio of  $\text{CaSO}_4$  Hemi and decreasing the ratio of  $\text{CaSO}_4$  Di attained slightly longer setting times. Though further study is needed for proof, the sudden jump in setting times for ratios higher than 50:50 may revolve around the ability of  $\text{CaSO}_4$  Hemi and Di to set and crystallize in each other's presence on a molecular level, and the subsequent effects of M and R on that setting reaction.



**Figure 1:** Setting Time of  $\text{CaSO}_4$  Mixtures, Hemi:Di

**Conclusions:** M and R greatly affected setting times of  $\text{CaSO}_4$  Hemi and Di mixtures of different ratios. A ratio of 60:40  $\text{CaSO}_4$  gave the most clinically useful working time. R affected the setting times in low concentrations of Hemi. However, it did not affect setting time as Hemi ratio increased. Interestingly, M greatly increased the setting time in all groups, perhaps due to interference with the setting reaction. Though this study only evaluated two drugs, mixing and optimizing ratios of  $\text{CaSO}_4$  Hemi to Di combinations may be useful for delivery of other antibiotics for prophylactic care of osteomyelitis.

### References:

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