

MRI Visualization of Local Drug Delivery

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Introduction:

In cases of orthopaedic infection, debridement and local delivery of antibiotics are employed to control infection. While a rare occurrence, the incidence of severe orthopaedic infection is increasing every year as the number of implant surgeries increases. The distribution of antimicrobials in vivo from local delivery is not well understood. The current methods used to detect the distribution of locally delivered antimicrobials in vivo is to take limited biopsies and fluid samples from the wound [1], but without the knowledge of the drug distribution pattern. These techniques can only provide limited spatial information, thus are not usable to direct patient specific care. To address this issue, we have developed an imaging-based technique, using a gadolinium-marked small molecule, for monitoring the distribution of locally delivered antimicrobial from bone cement in extremity wounds that will enable real time analysis of drug concentration and adjustment of clinical management.

Methods:

Surgical procedure

Gd-DTPA mixed cement was prepared with 2g Gd-DTPA and 8 g poragen (xylitol) loaded Simplex P[®] bone cement [2]. Gd-DTPA cement was implanted in 2 different wounds, "Partial Thickness" or "Full Thickness", created in the hind limbs of 9 New Zealand White rabbits. The "Partial Thickness" wounds were created by removing 0.5 cm³ of quadriceps muscle, closest to the femur. The dead space was filled with 1 mL of the Gd-DTPA cement; Muscle, fascia lata, and skin were closed. The "Full Thickness" wounds were created by removing 1.0 cm³ of quadriceps muscle and removing a 1 cm x 4 mm window from the anterolateral aspect of the femoral cortex. The dead space intramedullary femur and muscle was filled with 1.5 mL of Gd-DTPA bone cement and an intramedullary Gd-DTPA cement rod. Skin was the only tissue closed in these wounds.

MR imaging protocol

MRI measurement was performed on a 7T Bruker Biospec small-animal scanner. Rabbits (body weight = 2kg±0.5kg) were under anesthesia with 2% isoflurane in oxygen, while body temperature was maintained at 37°C. Respiration, heart rate and blood oxygen level were monitored over the duration of the experiment. Variable repetition time (TR=5000ms, 3000ms, 2300ms, 1500ms) T1 weighted images were taken along axial direction with the following parameters: FOV=10cm, slice thickness=2.0mm, matrix=256x256, TE=11.0ms. RARE=4, total acquisition time=15 minutes. Fat suppression was used to suppress the fat signal in the muscle. Imaging geometry was carefully adjusted to avoid ghosting artifact from blood vessel artifacts to overlap the surgery region. One T1 weighted scan was performed prior to surgery, and a series of scans were performed immediately after the surgery, with 15-minute intervals, for 5.5 hours. T1 maps were calculated by an exponential fitting method. The area of contrast was segmented, based on the T1 maps with threshold at 2200 ms. The concentration of contrast was calculated in the segmented regions. Volumes of distribution of the locally delivered Gd-DTPA were calculated for each specimen and compared using a t-test, $\alpha=0.05$.

Results:

There is a statistically significant difference in both the volume of distribution of contrast agents ($p=0.001$) and total mass ($p=0.0006$) between images with contrast and images without contrast. The least visible contrast, where T1 value is 2200 ms, are converted to concentration using T10 values of the mean histogram value at pre-contrast, plus and minus a standard deviation of the histogram. The resulting concentration is 14 $\mu\text{g/mL}$ with a range of 26 to 0 $\mu\text{g/mL}$. It was found that higher concentrations have lower errors, with a mean concentration value of 2767 $\mu\text{g/mL}$, ranging from 2779 to 2745 $\mu\text{g/mL}$. In "Partial thickness wound model", the majority of contrast agent was found in the incision site, along intramuscular septa, and submuscular surrounding the femur (Fig 1c). In the case where the muscle was left open ("Full Thickness model") there was a large amount of contrast visible under the skin (Fig 1d), which was not the case when the muscle was closed.

Discussion:

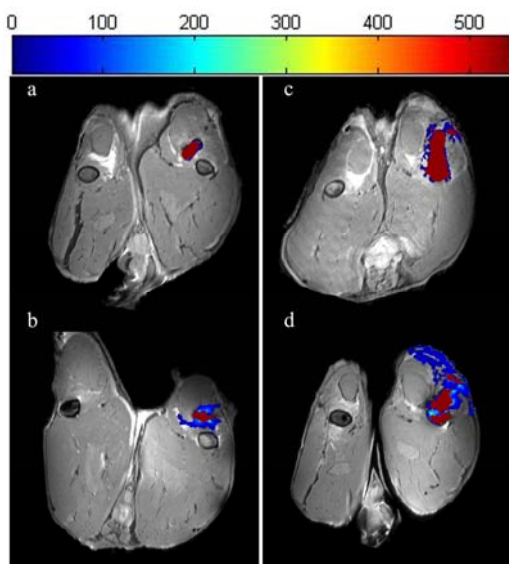
Most of the Gd-DTPA remained close to the delivery site in and around the muscle near the depot. The drug distributed anisotropically, giving preference to less dense spaces, and most importantly the dead space adjacent to the Gd-DTPA cement. Differences in tissue closure, (muscle and fascia lata), made a considerable difference in the final distribution of the drugs. This study shows the distribution of locally delivered Gd-DTPA varies greatly over locations, suggesting that the traditional biopsy and wound fluid assays methods may suffer more variation than previously appreciated. Tracking gadolinium marked small molecules under MRI can be a useful technique to provide detailed spatial and temporal information for local drug delivery.

Conclusion:

With MR imaging technique, the drug delivery from controlled release vehicles can be visualized and concentrations can be determined. Furthermore, this method produces practical results of clinical relevance.

REFERENCES:

1. Adams, K., et al. Clin Orthop and Relat Res, 1992. 278: p. 244-252.
2. Giers MB, et. Al. Clin Orthop Relat Res. 2012 Mar 23.



Concentration maps, in $\mu\text{g/mL}$, a) a control implant with no contrast and b) an experimental implant with contrast in a wound with muscle closed. c) a control implant with no contrast and d) an experimental implant with contrast in a wound with muscle left open. Red indicates areas of contrast above the visible range as well as the implant.