NUCLEAR SCINTIGRAPHY FOR EARLY DIAGNOSIS OF OSTEOMYELITIS IN AN INFECTED NON-UNION RABBIT MODEL

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Introduction: Osteomyelitis leading to infected non-union is a devastating complication following long-bone fracture repair. Early diagnosis and treatment is essential for a favorable outcome. Currently available imaging modalities have either low specificity or sensitivity. Many of these modalities are based on anatomical changes associated with osteomyelitis, which are also altered with fracture and surgery. Artifacts are introduced particularly when metallic implants are used. Nuclear scintigraphy is based on physiological rather than anatomical changes and may be beneficial for early diagnosis of postoperative osteomyelitis. An increase radiouclide uptake of technetium labeled phosphate (Tc-PO) is indicative of an increase in either blood flow or bone metabolism, which would occur with both fracture healing and osteomyelitis. However, technetium-labeled ciprofloxacin (Tc-CIPRO) binds specifically to bacterial DNA gyrase and is reported to have a high specificity and sensitivity for diagnosis of infection, including osteomyelitis. The objective of this study was to evaluate the use of Tc-PO and Tc-CIPRO for early diagnosis of osteomyelitis in an infected non-union model. The study was designed to test the hypothesis that the uptake ratio for Tc-PO and Tc-CIPRO would be higher in infected compared to non-infected fractures.

Methods: Thirty-two skeletally mature New Zealand White rabbits with a unilateral femoral defect stabilized with plates and screws were used. This study was part of a larger study evaluating the use of adenosine transfer of the bone morphogenetic-2 gene (Ad-BMP-2) for enhancing fracture healing in an infected non-union model. Experimental groups were: (1) non-infection Ad-Luciferase (Ad-LUC) control (NON-LUC), (2) non-infection Ad-BMP-2 treated (NON-BMP), (3) infected non-infection Ad-Luciferase control (INF-LUC), and (4) infected non-infection Ad-BMP-2 treated (INF-BMP). Rabbits in the infected groups were inoculated in the defect with Staphylococcus aureus, and quantitative aerobic culture was performed on all rabbits following euthanasia to confirm the presence or absence of infection. Nuclear scintigraphy was performed 4, 8, 12, and 16 weeks after surgery. The Tc-CIPRO (Infecton, IV Direct Ltd, London, England) scan was performed 48 hours after the Tc-PO (Oxidronate, Technescan-HDP, Mallinckrodt Medical, St. Louis MO) scan. The uptake ratio of the experimental (left, L) to normal (right, R) femur was calculated using the whole bone ROI and lateromedial and craniocaudal views. Rabbits were diagnosed as infected or non-infected based on subjective analysis of the Tc-CIPRO scan by a board-certified veterinary radiologist who was unaware of the experimental group assignment. In addition to quantitative aerobic culture, radiographic lysis grade at 16 weeks was used as a clinical outcome measurement of osteomyelitis. Data were analyzed using an ANOVA and Pearson’s Correlation. A p<0.05 was considered statistically significant. All procedures were approved by the Colorado State University Animal Care and Use Committee.

Essential Results: Tc-PO: A log-transformation was performed to normalize the data. There was a significant difference in Tc-PO uptake ratio between infected and non-infected fractures at 8, 12, and 16 weeks. The uptake ratio in infected fractures increased and non-infected rabbits decreased with time (Fig 1A). There was a significant association between the uptake ratio for both the whole bone ROI and Tc-CIPRO for evaluation of postoperative osteomyelitis following repair of long-bone fractures.

Discussion: The results of this study suggest that Tc-PO and Tc-CIPRO may be useful for diagnosing osteomyelitis late in healing. The lack of a significant difference between infected and non-infected fractures with Tc-PO in the early postoperative period was expected because of the increase in blood flow and bone metabolism associated with the recovery of the fracture and healing. The lack of significance with Tc-CIPRO in early healing was not expected and is difficult to explain because of the previously reported high specificity and sensitivity. The high false positive results (Fig 3) may be a result of an increase in blood flow to the fracture site, a decrease in venous drainage, or obstruction of Tc-CIPRO to something other than bacteria. False negative results may result from areas of ischemia or abscission. Future studies involving scanning at a longer period post-injection and earlier in the course of fracture healing are required to evaluate the usefulness of Tc-CIPRO for evaluation of postoperative osteomyelitis following repair of long-bone fractures.


Fig 1. Plots showing the association between the log of the Tc-PO uptake ratio and infection (A) or radiographic lysis grade (B) using the whole bone ROI and lateral view. Lysis grade 0=none, 1=slight, 2=mild, 3=moderate. Different letters represent statistically significant differences. The level of significance was p<0.05.

Fig 2. Plots showing the association between Tc-CIPRO uptake ratio and infection (A) or radiographic lysis grade (B) using the whole bone ROI and lateral view. Lysis grade 0=none, 1=slight, 2=mild, 3=moderate. Different letters represent statistically significant differences. The level of significance was p<0.05.

Fig 3. Lateromedial view of Tc-CIPRO scan illustrating an increase in uptake in both infected (A) and non-infected (B) rabbits at 4 weeks. The uptake in infected rabbits either remained constant or increased with time (not shown) and the uptake in non-infected rabbits decreased with time and was minimal at 16 weeks (C). The arrow shows the operated (left) femur, and the contralateral (right) femur was used as a control.