Care and Use Standards for the Development of an Animal Model of Periprosthetic Joint Infection

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Introduction: Animal models are useful and required for mechanistic and translational aspects of disease. While outcomes assessed using these models are usually the focus, the care of these animals during and after these experimental procedures can be critical in reproducibility and ethical treatment of animals. In this study, we compiled data on the care and use of rabbits during development and treatment of a periprosthetic joint infection (PJI) model in order to give recommendations for the care of these animals in vigorous surgical procedures.

Methods: From September 2018 to July 2022, a total of 11 experiments with 71 female New Zealand white rabbits (purchased from Charles River and Envigo) were completed to develop the PJI rabbit model and to test treatment strategies. Rabbits underwent a tibial hemiarthroplasty followed by inoculation with *Staphyloccocus aureus.* After two weeks, rabbits underwent various local treatment strategies. Rabbits were euthanized two weeks after treatment for outcome analysis. Manual rabbit chart review was conducted to collect weight changes during the study period, surgical duration, anesthesia, post-operative care, and complications. This study was approved by the Institutional Animal Care and Use Committee and Institutional Biosafety Committee.

Results: Surgical time decreased with increased experimental experience for the anesthesia and surgical team (Figure 1A). Animals lost weight from index surgery to treatment surgery (p=0.0001, Figure 2A) where increased mortality was seen during treatment surgery (p=0.044, Figure 2B). These anesthesia related mortalities may not be related to index (p=0.844) or treatment weight (p=0.575), although these analyses were underpowered**.** Nevertheless, index weight >4 Kg was implemented to encourage increased survival during treatment surgery. Subcutaneous supplementation with saline after surgery and post-operative day (POD)-1 and 2 was provided to help with post-operative dehydration. Bandage removal two to four days after surgery did not increase surgical site infection rates, decreased bandage-induced leg swelling, and increased rabbit mobility by subjective veterinary staff observation. Post-operative supplemental care included hay, vegetables, fruits, probiotics, DietGel Recovery/Critical Care, and Prang, an oral rehydrate. For those rabbits that were having trouble with eating, addition of thiamine in early studies and capromorelin in later studies was used for appetite stimulation. Blood collected prior to surgical procedures required constant rotation during storage even with the addition of anti-coagulation additives. Addition of these optimizations led to trending increased survival in experiments, although not significant with this small sample size (p=0.338, Figure 3).

Discussion: The lessons learned and implemented regarding the care of rabbits during this PJI model has led to healthier rabbits trending toward less mortality compared to earlier studies. This study has combined peri- and post-operative data to optimize care for rabbits undergoing invasive surgical procedures and allowed us to share our best practices with other groups implementing studies with these animals.

Significance/Clinical Relevance: While animals are used for outcomes assessment, standardization of the care of these animals during experimental procedures and post-operative care are critical in reproducibility and ethical treatment of animals.

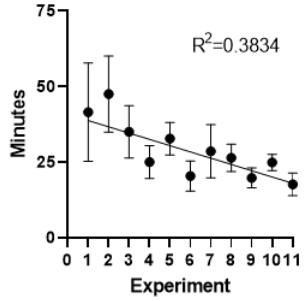

Figure 1. Index surgery surgical time throughout experiments Average surgical time from incision to closure depicted in minutes.

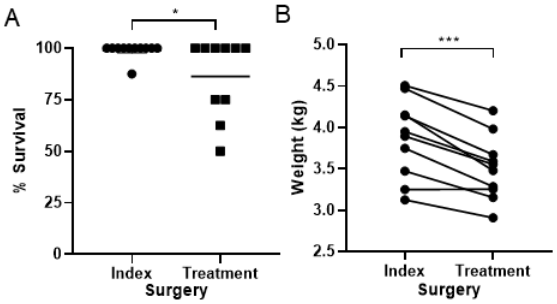

Figure 2. Weight and Survival During Surgery (A) Average weight and (B) percent survival of each experiment during index and treatment surgery. (C) Index weight and (D) treatment weight of each animal and their survival. N=71 animals from 11 experiments * p<0.05; *** p<0.001

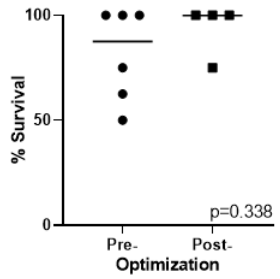

Figure 3. Care Optimization and Survival Each point represents an experiment and percent survival through the four-week study period before or after care optimization was implemented. n=10 experiments* with 69 rabbits used for survival percentages.*One experiment was omitted with n=2 rabbits since it was a two-week experiment with no treatment.