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A Case Study Comparison of Two Preclinical Studies Utilizing Traditional Versus Modified Methods for Surgical Closing and Post-Operative Treatment for Muscle Biopsy Sites in Nonhuman Primates

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ABSTRACT

Muscle biopsy in nonhuman primates is a specialized collection procedure for samples that can be utilized to diagnose or monitor certain diseases and/or assess biodistribution in tissue. The procedure carries an inherent risk of post-operative complications including dehiscence and infections due to animal movement, grooming, and environmental conditions of group housing.

The traditional method utilizes absorbable sutures to close muscle and skin, with optional surgical adhesive for skin. Standard post-operative care included administration of a non-steroidal anti-inflammatory, limited social contact, daily surgical site observations, and potential antibiotic administration, if indications of post-operative infection develop. However, evolving study designs, including multiple sample collections and housing animals in corrals, compared to cages, led to a higher rate of operative complications and introduced confounding variables to toxicology studies. Modifications were made to the post-operative procedures to reduce the duration of single housing, allow the surgical site to withstand greater activity levels (including grooming), and reduce post-operative complications.

In the modified method, the muscle was closed using absorbable sutures and the skin was closed using absorbable sutures, surgical staples, and optional surgical adhesive to reduce dehiscence. After completion of the procedure, a prophylactic, long-acting antibiotic and non-steroidal anti-inflammatory were administered globally.

With these modifications, animals could be returned to social housing immediately and post-operative complications including dehiscence, discharge, and site swelling decreased from 7% of biopsy sites to less than 1% of biopsy sites. Moreover, it eliminated the need for revision surgery and reduced confounding variables with inconsistent antibiotic administration.

NEW PROCEDURE

1. Sterilized all instruments in autoclave prior to procedure.
2. Anesthetized the animal with intramuscular ketamine (10 mg/kg) and dexmedetomidine (0.05 mg/kg).
3. Administered pre-analgesics, meloxicam (0.2 mg/kg).
4. Shaved area around collection sites and cleaned with antiseptic solution and alcohol.
5. Placed the animal on lateral recumbency and cleaned the shaved area with a surgical scrub.
6. Made skin incision over the selected muscle. Used blunt dissection to expose the selected muscle.
7. Placed the cutting edge of the punch lightly on the muscle, perpendicular to the intended biopsy site, and depressed the muscle with the punch using firm pressure.
8. Rotated the punch until resistance stopped and the muscle returned to its original position. Used metzenbaum surgical scissors to collect sample and placed into vial/container.
9. Transferred collected sample to lab for processing.
10. Applied firm pressure to surgical area with sterile gauze until the biopsy site reached homeostasis.
11. Closed muscle and skin using a simple interrupted suture pattern with 3.0 polyglycolic 910 synthetic absorbable suture.
12. Applied surgical staples and surgical adhesive.
13. Administered bupivacaine (1 mg/kg) subcutaneously at the incision sites and ceftiofur (20 mg/kg) subcutaneously.
14. Administered atipamezole (0.25 mg/kg) to reverse anesthetic effect of the dexmedetomidine.
15. Administered meloxicam (0.2 mg/kg) intramuscularly once a day for 2 days post-operatively.
16. Observed biopsy site and animal demeanor for approximately 7 days following the procedure.

Collection Site Images Showing Collection to Healing

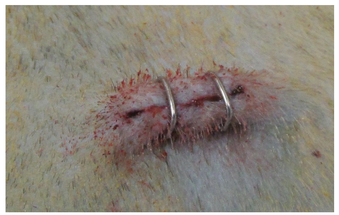

Figure 1. Muscle biopsy immediately after procedure utilizing the new procedure (day 0).

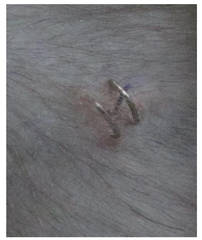

Figure 2. Muscle biopsy post healing period, after utilizing the new procedure, prior to staple removal (day 14).

Figure 3. Muscle biopsy post healing period after utilizing old procedure techniques (day 24).

RESULTS

In previous studies, sutures and surgical glue were deemed adequate in keeping incisions closed until fully healed, but this approach has in recent years been proved to be insufficient as a result of social grooming in group housing that has in turn lead to increased animal activity.

It is essential that animals receive the full benefit of group housing, and therefore, we updated our already established procedures to address the main issues that had been observed: dehiscence, infection, and inconsistent antibiotic administration that could impact study outcomes. Adding surgical staples proved to be secure enough to handle the increased activity and social grooming and the ceftiofur was sufficient to mitigate any post-operative infections uniformly across animals before any additional treatment was needed. Therefore, the animals could be returned to group housing within 24 hours after the procedure to resume socialization. As shown in **Table 1**, several complications were encountered in the case studies presented.

In the case studies presented, collection was from two muscle sites at each collection timepoint (gastrocnemius and vastus lateralis) for a total of four muscle punch biopsies per surgery timepoint. These minor procedure changes allowed for two 8 mm biopsy punch samples to be taken per muscle site per 14-day period safely which was previously limited to a 21-day period. This was due to reduced overall healing time. Furthermore, this operational change can contribute to an overall reduction in animal use on future studies as more collections can be safely obtained from the same animals instead of increasing cohorts or group sizes to achieve the same number of collections.

Table 1. Instances of Types of Complications Encountered in Case Study of Two Toxicology Studies with Muscle Biopsies

	New Procedure Techniques Study		Old Procedure Techniques Study	
Issue	Number of incidences	Percent of biopsies effected	Number of incidences	Percent of biopsies effected
Dehiscence	1	0.89%	8	5.5%
Discharge	0	0	6	4.2%
Site Swelling	0	0	6	4.2%

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The case studies utilized in this review were multi-dose toxicity studies of test articles of the same drug class.