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Intravenous Sampling and Administration in Rodents: Overcoming the Challenges in the Use of Vascular Access Buttons™ in Rodents

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ABSTRACT

Repeated reliable access to the vascular space in rodents can be challenging in preclinical modeling. Vascular access buttons (VAB) offer a solution as permanent transcutaneous catheters for blood collection and dose administration in a closed system. In chronic toxicological studies, long-term catheter patency is crucial, and VABs also reduce stress and allow for group housing. However, a retrospective review of multiple studies revealed the need for modifications to ensure successful studies, prolonged catheter patency, and data collection.

During a study prior to those implementations, around 9% of VAB-implanted animals required veterinary treatment unrelated to the test article leading to important histopathological findings and unscheduled euthanasia. Subsequent studies reduced the frequency and intensity of such observations. Changes in animal care included an extended acclimation period, regular surgical site cleaning, patency checks, nail trimming, and adjustments in husbandry practices like using cellulose bedding, more frequent nail trims, and modifying food hoppers and enrichment items.

These modifications successfully reduced surgical site inflammation and mortality. However, subsequent studies lacked histopathologic evaluation and/or had smaller animal populations, preventing examination of associated findings such as injection site inflammation and thrombi. Larger studies are needed to implement the modifications and conduct comprehensive pathological evaluations. This will help identify further adaptations and establish comparative reference ranges for clinical pathology and histopathology in surgically implanted animals, providing valuable background data for future research.

BACKGROUND

Vascular access buttons (VAB) offer a permanent transcutaneous catheter solution for blood collection and dose administration in a closed system. In chronic toxicological studies, long-term catheter patency is crucial to maintain access to the vasculature and allow for repeated sampling and dosing. The use of a closed system, like VAB, allows for social group housing, an important animal welfare factor, while also contributing to stress reduction by promoting more freedom of movement due to shortened and less restrictive restrain compared to traditional rodent restrainers.

This retrospective review of multiple studies, conducted at our Testing Facility in Everett, Washington, summarizes several modifications made based on the experience with the model to ensure successful studies, prolonged catheter patency, and good-quality data collection.

Table 1. Sample table

Number of animals in study	Swelling	Scab and crust	Discharge	Antibiotic	Anti-inflammatory	Found dead or euthanized
20	35.0%	15.0%	5.0%	-	-	-
30	3.3%	13.3%	6.7%	-	-	-
60	20.0%	8.3%	-	-	-	-
92	18.5%	20.7%	5.4%	4.5%	8.7%	8.7%
204	2.9%	2.9%	0.5%	-	3%	3%
38	7.9%	23.7%	2.6%	-	5.3%	-
12	-	-	-	-	-	-
48	16.7%	25.0%	4.2%	-	-	4%
180	0.6%	2.8%	0.6%	-	-	-

Figure 1. Seroma surrounding the VAB implant surgical site in a female rat, side view.

METHODS

During this review, 9 studies with a total of 664 VAB-implanted rats and 20 VAB-implanted mice were identified between 2022 and 2023. The acclimation phase was selected for evaluation to remove potential confounding factors relating to dose administration. The duration of the acclimation phase was variable, and findings ranged from Day -49 to Day -1 predose. Veterinary Service Requests (VSRs) were also reviewed and screened for findings related to inflammation of the implant surgical site and to see if treatments were required. Clinical observation and veterinary treatment data were reviewed and tabulated to evaluate the frequencies of animals presenting with swelling, discharge, scabs, and crust, those requiring treatment with antibiotic or anti-inflammatory, and animals found dead or euthanized due to VAB-related causes as shown in Table 1.

OBJECTIVE

This review objective was to identify areas of potential improvement in using VAB-implanted animals relating to animal welfare and minimizing non-test article-related findings commonly associated with this test system. A comparison was made of common findings associated with the VAB implant, such as swelling, scabbing, and discharge of the surgical site prior to and during the implementation of current practices.

MODIFICATIONS

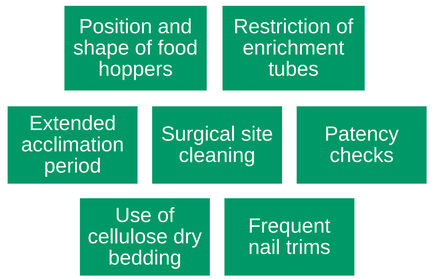

Figure 2. Modifications implemented to reduce VAB-associated inflammation and morbidity.

RESULTS AND DISCUSSION

Common findings, across studies, included swelling, discharge, scab, and crust formation around the implant's surgical site noted at various severities. Animals found dead or routed for unscheduled euthanasia accounted for 2% of all rats used during the acclimation phase. Overall, prior to the modifications discussed in the following section, around 9% of VAB-implanted animals required veterinary treatment unrelated to test article that were associated with inflammation of the VAB-implant site. Subsequent studies presented a reduction in the frequency and intensity of such observations.

Some significant changes were noted following simple husbandry modifications, such as the shape and position of food hoppers and the restriction of enrichment tubes. The use of regular rodent caging supplies was associated with a higher risk for avulsion of the magnetic button and the use of modified cage supplies allowed for free movement of the animals and reduced trauma to the implant area. Also, of note in husbandry procedures, the bedding material was substituted for a dry cellulose bedding to reduce dust accumulation in the implant surgical site.

Extension of the acclimation duration has also contributed to implementing routine cleaning of the surgical site, as well as more frequent nail trimming following the arrival of animals from the vendor. This period allowed for monitoring and veterinary intervention, as needed, and provided the animals additional recovery time post-surgical implantation. Animals, observed with persisting swelling or discharge, can be removed from a study, thus reducing model interference during the dosing period.

A significant reduction in the need for veterinary treatment was observed following the implementation of new practices, despite a similar frequency of observations of swelling, scabbing, and discharge. This was attributed to a reduction in the severity of inflammation and was associated with a reduction in the frequency of animals requiring unscheduled euthanasia and/or being found dead.

Figure 3. The hopper is located on the side of the cage and extends to the bottom to allow for easy access to food while reducing the risk of dislodging the button or cap.

CONCLUSION

These modifications successfully reduced the severity and frequency of surgical site inflammation and moribundity associated with VAB surgical implants. The baseline incidence of these findings aided in guiding the number of spares needed per study in comparison with non-implanted animals and helped contribute to continued process improvement in support of the 3Rs.

Nonetheless, this review does not include a comprehensive comparative clinical pathology and histopathology evaluation of potential implant- and catheter-associated findings, such as increases in white blood cells, fibrinogen and haptoglobin, granulomas, injection site inflammation, and thrombi. The persistence of such findings, following the implementation of changes with considerable improvement of clinical observation, veterinary treatment, and morbidity, could indicate the need for further adaptations and help establish comparative reference ranges for clinical pathology and histopathology in VAB surgically implanted animals, providing valuable background data for future research.

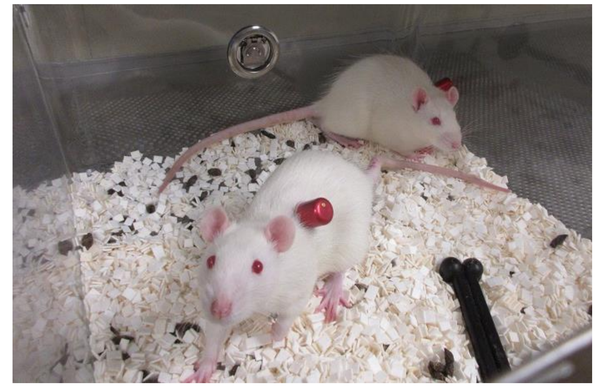

Figure 4. Socially housed VAB-implanted rats. Dry cellulose bedding and enrichment chew toy.

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