

# Embryo/Fetal Development Study in Rabbits via Continuous Intravenous Infusion: Refinements to Infusion Systems and Procedures to Increase Study Efficiency and Improve Animal Welfare

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## 1 ABSTRACT

Continuous Intravenous (IV) Infusion in pregnant rabbits is a challenging route of administration. Traditional methods include surgical placement of the catheter in a femoral vein with a side access vascular port placed subcutaneously in the scapular area. Maintenance of the port requires transcutaneous needle introduction and dose administration requires placement of a dosing catheter via a large introducer needle into the port in unanesthetized pregnant rabbits. A pilot study was conducted to evaluate the feasibility of using jugular vein catheters attached to transcutaneous buttons with magnetic connections. As the button protrudes out of the back of the rabbit, the first step was collaborating with vendors on refinements to the jackets and magnetic injectors for dosing. Twenty-one female New Zealand white rabbits were surgically implanted with round tip jugular vein catheters bonded to transcutaneous buttons which were placed in the scapular area. Following a 14-day recovery period, twenty females were bred (1:1) with naïve resident males. The females were dosed with 0.9% sterile saline via continuous IV infusion at a rate of 0.5 mL/kg/hour from gestation days 7 through 20, inclusively. Clinical observations, body weights, food consumption, macroscopic examinations, gravid uterine weights and external fetal morphology were evaluated in addition to catheter placement, patency, and dose syringe weights. Minimal body weight losses and/or gains, with corresponding minimal changes in food consumption, were noted for all females during the dosing period. At necropsy, 19 (of 20) females were gravid and intrauterine growth, survival and external fetal morphology were within the range of laboratory historical control data. Clinical observations including mild jacket-associated irritation that was transient and did not impact overall animal health. All animals had patent catheters throughout the dosing period. The use of transcutaneous buttons with magnetic connections proved successful in this study. This technique provided an improvement to animal welfare and study efficiency because it eliminated transcutaneous needle introductions, and the button could be accessed quickly with minimal restraint and handling of the animals.

## 2 MATERIALS AND METHODS

- ❑ 22 nonpregnant female New Zealand White rabbits were procured (Envigo Global Services, Inc., Denver, PA).
- ❑ Rabbits were identified with a microchip and acclimated to the facility and jackets for 10 days.
- ❑ Each rabbit was surgically implanted at the Testing Facility with a round tip jugular vein catheter bonded to a transcutaneous button which was placed in the scapular area.
- ❑ The transcutaneous button stands above the back of the rabbit (Figure 1) so refinements to infusion equipment and jackets (based on a previous pilot study) included the use of a 90-degree injector surrounded by a neoprene collar. (Figure 2)
- ❑ A jacket and/or protective collar was placed on each animal prior to return to its home cage.
- ❑ Following a 14-day post-surgery recovery period, implanted females were mated with naïve resident males of the same strain and source according to Testing Facility SOPs.
- ❑ Successfully mated females were dosed with 0.9% sodium chloride for injection via continuous IV infusion at a rate of 0.5 mL/kg/hr from gestation days 7 through 20, inclusively, using a small ambulatory infusion pump contained within a pouch attached to the jacket on the back of each animal (Figure 3).
- ❑ Endpoints evaluated: Clinical observations, body weights, food consumption, gravid uterine weights, macroscopic findings, ovarian and uterine examination, and external fetal morphology. Catheter placement, patency, and dose syringe weights were also collected.



Figure 1: Post-surgery button with protective cap.



Figure 3: Ambulatory infusion pump



Figure 2: 90-degree injector with neoprene collar.

## 3 RESULTS

- ❑ Surgery/Infusion Patency: All females were successfully surgically implanted and noted with unidirectional patency throughout the study which allowed for infusion (but not blood draw); 8 females were bidirectionally patent.
- ❑ Survival: all females survived to scheduled termination with one exception. A single female was euthanized for humane reasons following a post-surgery in-cage injury.
- ❑ Maternal Performance: mating was not impacted by the presence of the transcutaneous button. Twenty out of 21 females successfully mated with a male (19 out of 20 were gravid).
- ❑ Clinical Observations: generally limited to jacket-associated irritation (red skin discoloration, swelling, and/or scabbing), which were transient and/or had no impact on overall health or infusion delivery.
- ❑ Body Weights and Food Consumption: minimal body weight gains ( $\leq 151$  g) or body weight losses were noted for all females throughout the infusion period; however, this is a consistent observation for jacketed animals. Low food consumption (23 to 118 g/day) was observed for 8 females during the dosing period.
- ❑ Macroscopic Examination: No remarkable macroscopic observations were noted at necropsy. Catheter tips were in place for 18 females while the remaining 2 were located in the jugular anastomosis which had no impact on infusion.
- ❑ Intrauterine Growth and Survival, and Fetal Morphology: Mean gravid uterine weight, and ovarian and uterine examination data were similar to historical control. No external fetal malformations or variations were observed.

## 3 RESULTS (cont'd.)

Parameter	Button-Implanted Rabbits Mean	CRL Historical Data Mean (Range)
Gravid Uterine Weight	510.58	499.43 (420.09 – 565.27)
Mean No. Corpora Lutea	11.0	10.00 (8.79 – 11.41)
Mean No. Implantations	9.0	9.18 (7.86 – 10.53)
Preimplantation Loss (%)	16.9	8.03 (1.14 – 21.56)
Viable Fetuses/Litter	8.8	8.78 (7.35 – 10.16)
Mean No. Resorptions	0.2	0.4 (0.05 – 1.05)
Postimplantation Loss (%)	2.52	4.41 (0.6 – 11.86)
Mean Fetal Weight (g)	43.37	41.302 (36.36 – 44.58)

## 4 CONCLUSIONS

The use of a transcutaneous button with a magnetic connection proved successful in this embryo/fetal development study and was an improvement to animal welfare and study efficiency.

- ❑ Surgical implantation of jugular vein catheters with transcutaneous buttons was less invasive, and surgical recovery was improved over previous methods with femoral vein catheters.
- ❑ Access to transcutaneous buttons and infusion system for maintenance and dosing was a non-invasive procedure and was less stressful on the animals (and also the staff) compared to previous methods involving skin parallel vascular access ports.
- ❑ Modifications to the magnetic injectors and jackets were successful and improved efficiency for continuous infusion dosing in rabbits.

