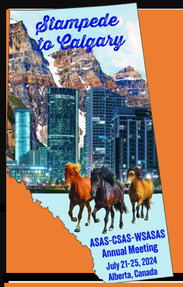

Assessment of the effective tissue concentrations of injectable lidocaine and a lidocaine-impregnated latex band for castration in calves and lambs

Authors: Joseph A. Ross [1], Steven M. Roche [2], Kendall Beaugrand [1], Crystal Schatz[1], Ann Hammad[1], Brenda J. Ralston[3], Andrea M. Hanson[3], **Nicholas Allan**[1], Merle Olson[4,1]

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Author Affiliations

1. **Chinook Contract Research Inc.**
2. **ACER Consulting Ltd.**
3. **Lakeland College**
4. **Alberta Veterinary Laboratories Ltd/Solvet**

Objectives

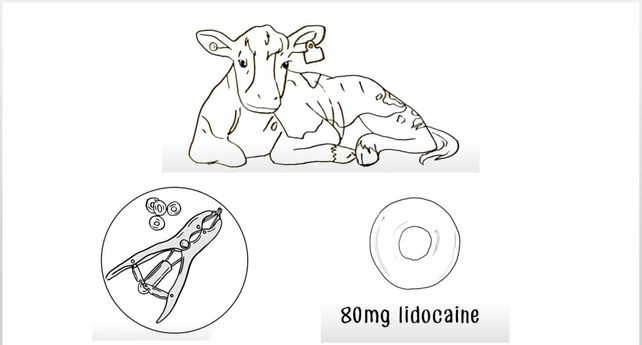
The purpose of this study was to assess the effective tissue concentrations of the current standard of care for pain mitigation in calves and lambs during castration or tail docking (injectable lidocaine) and to assess the ability of a lidocaine-loaded elastration band (LLB) to deliver effective concentrations into the scrotal or tail tissues over time.

Abstract and Background

Chinook Contract Research Inc. (CCR) has developed a novel anesthetic-delivering elastration ligation band. The Care-Ring™ Technology (US Patent # 11,596,510) can be used with all current elastrator tools. It has been designed to deliver a clinically relevant therapeutic dose of anesthetic for the duration of its application(s). CCR has partnered with Alberta Veterinary Laboratories/Solvet (AVL/Solvet) to manufacture the device as the LidoBand™ in Alberta. In 2022, RDAR supported a research project (2022N090R) directed by Alberta Lamb Producers to adapt this novel made-in-Alberta welfare technology for use in Alberta's lamb industry for welfare friendly tail docking and castration applications. This poster presents some of the results from four different trials in both lambs and dairy calves: 1) investigation of *in vitro* release of lidocaine from LidoBands; 2) pharmacokinetics (PK) and pharmacodynamics (PD) of injectable lidocaine in scrotal and tail tissue; 3) pharmacokinetics and pharmacodynamics of in vivo delivery of lidocaine with LidoBands placed on the tail and scrotum of lambs; and 4) a "proof-of-concept" study comparing the sensation of control- versus LidoBand™-banded tail tissue over time.

KEY RESULTS:

- **Lidocaine EC_{50} 0.17 mg/g tissue for Lamb Scrotums**
- **Lidocaine EC_{50} 0.077 mg/g tissue for Lamb Tails**
- **Lidocaine EC_{50} 0.54 mg/g tissue for Calf Scrotums**



Alberta Lamb Producers

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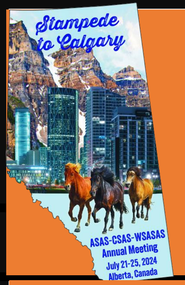

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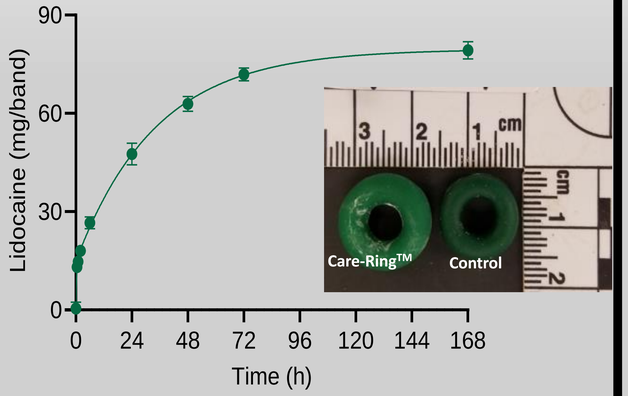
In vitro Release Kinetics & Device Design



$K_{obs(fast)}$ = 2.98 (95% CI: 1.81-6.70) mg·h^{-1}
$K_{obs(slow)}$ = 0.0292 (95% CI: 0.0266-0.0320) mg·h^{-1}
Y_{Max} = 79.6 (95% CI: 77.8-81.4) mg·band^{-1}
Percent fast = 18.11 (95% CI: 15.5-20.8)

The Care-Ring™ technology was specifically designed to deliver lidocaine rapidly (to address acute discomfort) and for a prolonged duration (to address chronic discomfort).

RESULTS: A dissolution experiment using USP<711> was used to quantitate *in vitro* release of lidocaine over a 1-week time course. Lidocaine release was initially rapid (K_{obs} = 2.98 mg/hour) for the first 30.4 hours of the time course, slowing to 0.0292 mg/hour for the remainder.

Methods

This work comprised four different field trials (n=50/trial): (1) effective concentrations of injectable lidocaine in the scrotal tissue of dairy calves; (2) the *in vivo* delivery of effective concentrations of lidocaine from LLBs placed on the calf scrotums; (3) effective concentrations of injectable lidocaine in the scrotal and tail tissue of lambs; and (4) the *in vivo* delivery of effective concentrations of lidocaine from LLBs placed on the lamb scrotums and tails. Sensation in the tissue of interest was assessed by electrocutaneous stimulation. Sensation was correlated to tissue concentrations of lidocaine by analyzing sampled tissue for lidocaine content by High-Performance Liquid Chromatography (HPLC).

Baseline Electro-Stim Measurement

↓

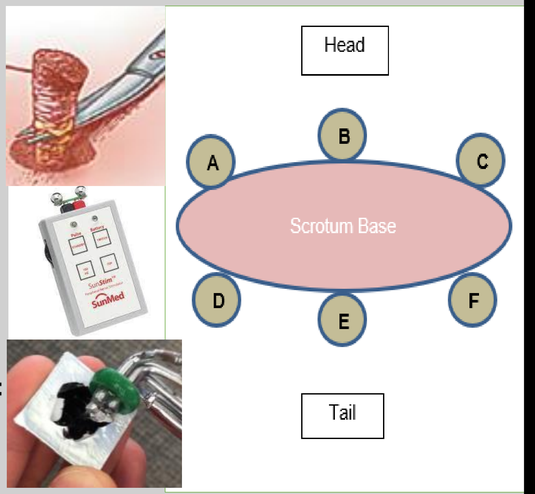
Marked 6 spots around the scrotal neck (lambs, calves) or the caudal fold of the tail (lambs).

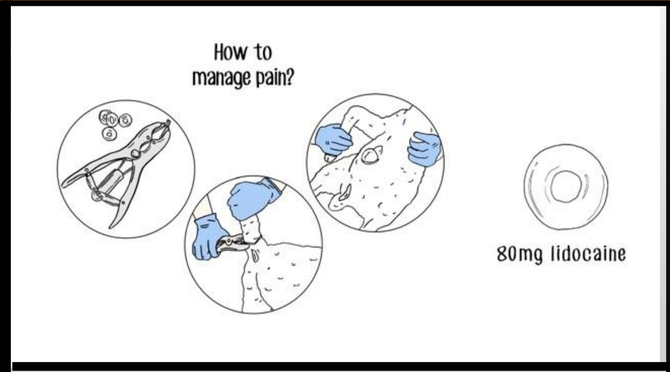
↓

Injected each spot with 2% w/v Lidocaine (without epinephrine) to establish a "ring block" (T=0)

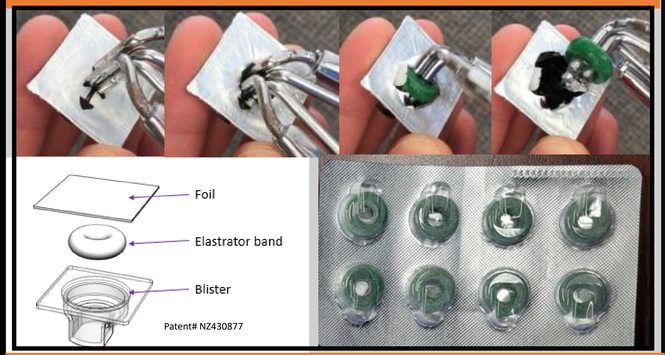
↓

At each time point post-injection (T=30, 60, 90, 120, 180, and 240 min):
- **Assessed sensation by Electro-Stim**
- **Removed a 4-mm punch biopsy to quantitate lidocaine levels**





Custom Packaging Design for Handling Safety and Efficacy



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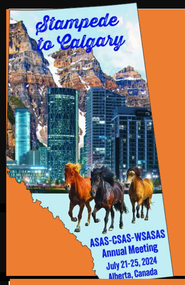

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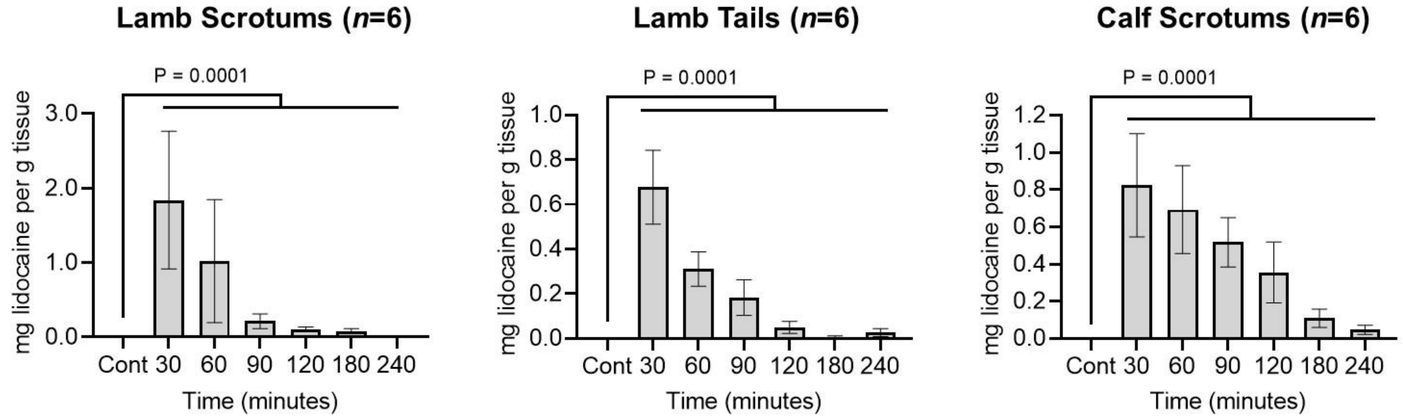
(A) Injectable Lidocaine PK in tissue

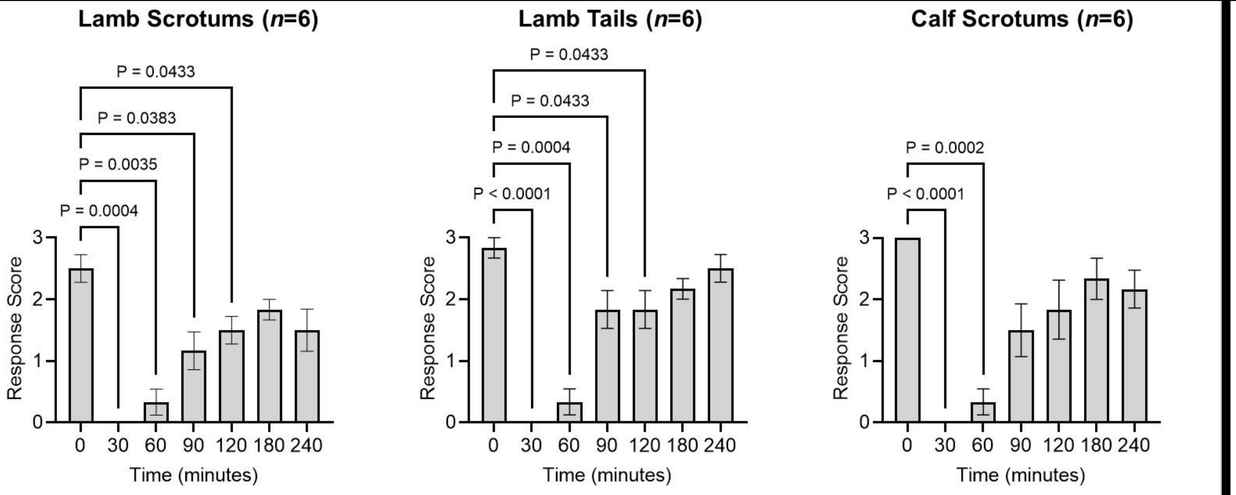


RESULTS: (A) Tissue lidocaine concentration for Calf or Lamb Scrotums or Lamb Tails at the indicated times after lidocaine injection (T = 0). **(B)** Electrocutaneous Stimulation Response Scores for Calf or Lamb Scrotums or Lamb Tails at the indicated times after lidocaine injection (T = 0). *P*-values were determined for each time-point relative to the T = 0 control sample using a repeated measures one-way ANOVA and corrected for multiple comparisons using Dunnett's test. Bars represent the mean ± SEM for 6 animals. **(C)** Stimulation response scores were plotted (on the *y*-axis) versus tissue lidocaine concentrations detected (on the *x*-axis) and non-linear regression was used to calculate the EC_{50} and EC_{95} values for Calf or Lamb Scrotal or Lamb Tail tissues.

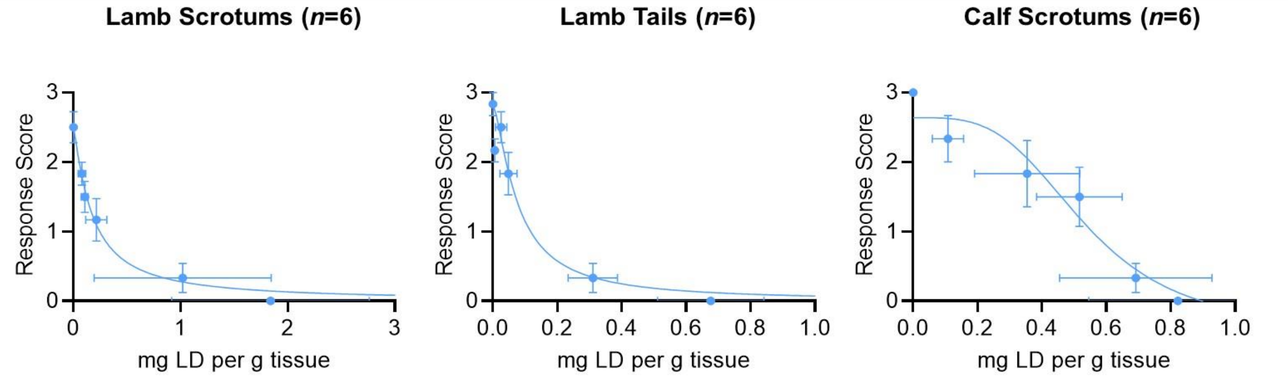
CONCLUSIONS:

- **Injectable Lidocaine onset of anesthesia within 30 minutes**
- **Injectable Lidocaine effect lasts up to 120 minutes**
- **EC50 in lamb scrotum is 0.17 mg/g tissue**
- **EC50 in lamb tails is 0.077 mg/g tissue**
- **EC50 in calf scrotums is 0.54 mg/g tissue**

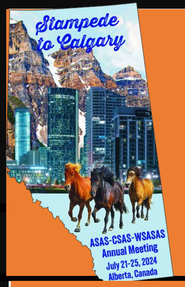
(B) Injectable Lidocaine sensation (PD)



(C) Estimation of Effective Concentrations



	Lamb Scrotums (*n*=6)	Lamb Tails (*n*=6)	Calf Scrotums (*n*=6)
EC_{50} =	0.17 (95% CI: 0.12-0.25)	0.077 (95% CI: 0.053-0.11)	0.54 (95% CI: 0.35-0.74) mg/g
EC_{95} =	2.1 (95% CI: 0.71-8.2)	0.61 (95% CI: 0.12-2.1)	1.2 (95% CI: 0.68-6.9) mg/g



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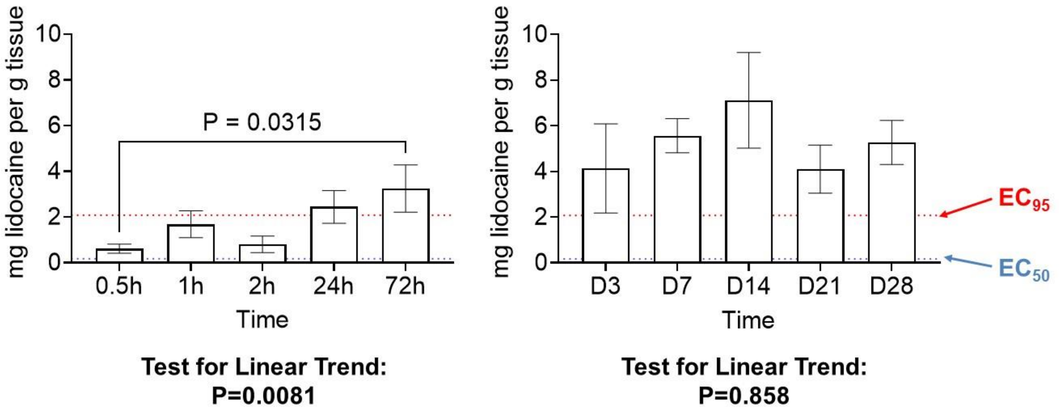
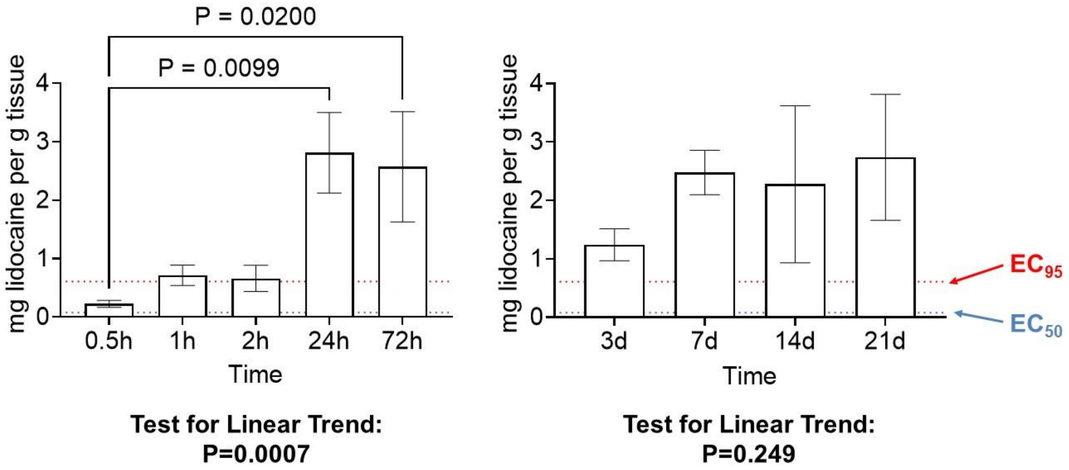
(A) LidoBand™ Lidocaine PK in lamb scrotal tissue

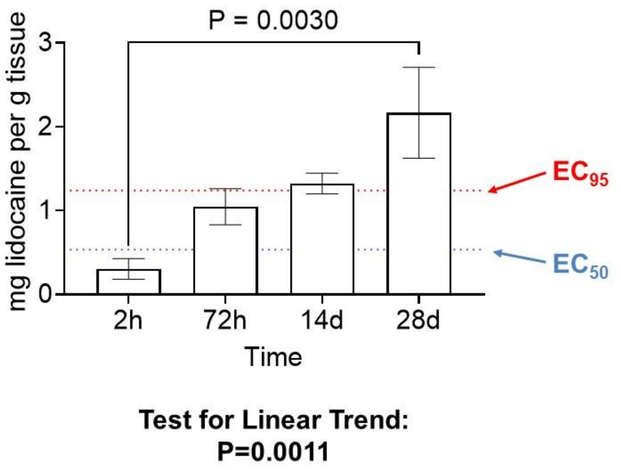


(B) LidoBand™ Lidocaine PK in lamb tail tissue



RESULTS: Lidocaine Levels in Calf or Lamb Scrotal or Lamb Tail Tissues Biopsied at the Indicated Times After Banding with LidoBands (LLBs). Acute time-points were assessed in an initial study, followed by chronic time points in a follow-up study. In all cases, bars represent the mean ± SEM of 5 animals (note that a different set of animals was tested for each time-point). *P*-values (relative to the earliest time point) were determined with a one-way ANOVA and corrected for multiple comparisons using Dunnett's test. For reference, the dotted lines denote the 95% CI of the EC_{50}. No lidocaine was detected in tissue from control-banded animals (not shown).

(C) LidoBand™ Lidocaine PK in calf scrotal tissue



Conclusions

This study defined the effective concentrations of injectable lidocaine yielding 50% or 95% reductions in local sensation (EC_{50} and EC_{95}, respectively). Injectable lidocaine allowed for short-term anesthesia for up to 120 min in calves, highlighting the importance of finding additional strategies to mitigate long-term pain. The use of the Care-Ring™ technology could provide an alternative. Here we demonstrated the LLB delivered tissue lidocaine concentrations that reached effective concentrations within as early as 30 minutes and met or exceeded the EC_{95} for at least 21-28 days.

Further field and laboratory studies into LidoBand™ efficacy are ongoing, including a comparison of the use of an injectable local anesthetic to the LidoBands™.

Acknowledgments

The authors wish to thank their industry partner, Alberta Lamb Producers, for their support and participation in this work. We also wish to thank our funders, Results Driven Agriculture Research and the Canadian Agricultural Partnership, a five-year federal, provincial, territorial initiative. We also wish to thank Alberta Agriculture and Irrigation for continued access to facilities and equipment to support CCR's field and laboratory work for this project as well as Lakeland College for the support of research staff and students during the field study component of this work. These studies, when animals were used, were conducted in compliance with the animal care guidelines established by the Canadian Council of Animal Care and were approved by the Chinook Contract Research IACUC (A8217-03).