Clinical trial protocol: Efficacy of pain control strategies for very young calves disbudded with caustic paste

Winder, C.B.¹, T.J. DeVries², K.D. Lissemore¹, T.F. Duffield¹

¹ Dept. of Population Medicine, Ontario Veterinary College, University of Guelph, Guelph, Ontario, Canada, N1G 2W1
² Dept. of Animal Biosciences, Ontario Agricultural College, University of Guelph, Guelph, Ontario, Canada N1G 2W1

Contact: Charlotte Winder | winderc@uoguelph.ca | Dept. of Population Medicine, University of Guelph, 50 Stone Rd. E., Guelph, Ontario, Canada, N1G 2W1

Administrative information

This trial protocol was written in accordance to Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Checklist (Chan et al., 2012). Funding for this study was received from Boehringer-Ingelheim Animal Health, Dairy Farmers of Ontario, and the Ontario Ministry of Agriculture, Food, and Rural Affairs – University of Guelph Research Program. Grant proposals were written by CBW in collaboration with TJD, KDL, and TFD. Study sponsors and funders were not/will not be involved in study design, data collection, data management, analysis and interpretation of data, writing of the report, and decision of submission for publication.

Introduction

The use of local anesthetic together with NSAID analgesia have been shown to be most effective at reducing indicators of pain following cautery disbudding, such as pain behaviours, serum cortisol, and pressure sensitivity (Duffield et al., 2010; Faulkner and Weary, 2000; Heinrich et al., 2010). However, far less published literature has examined best pain control practices for caustic paste disbudding. Two studies have found that local anesthesia combined with NSAID analgesia were most effective (as compared to no treatment, or either given alone) at reducing pain cause by caustic paste disbudding (Stilwell et al., 2008; Winder et al., 2017). A survey of Ontario dairy producers found that while 62 % of producers reported use of local anesthesia and 24 % reported use of NSAID analgesia, the use of caustic paste for disbudding significantly reduced the odds that the producer used pain control (Winder et al., 2016). One reason which may explain the lack of use of pain control for caustic paste (as compared to cautery) is that an immediate
avoidance reaction is not seen when the method is applied, which can lead producers to assume that caustic paste does not cause pain. As well, while the two studies examining local anesthesia and NSAID analgesia for caustic paste tested calves that were on average 2 (Winder et al., 2017) and 4 (Stilwell et al., 2008) weeks of age (which follows label directions of use up to 8 weeks of age), many producers may use this product on calves very early in life. Informally, we hear the argument that very young calves do not feel pain, or have the same pain experience as older calves, although there is no evidence to suggest this assumption is true. In fact, there is debate regarding the effect of maturity of the hypothalamopituitary adrenal and inflammatory axis on the experience of pain, with some argument that pain may be greater in neonates (Hulbert and Moisá, 2015). A well designed clinical trial of pain control protocols for young calves would be of benefit to the industry, in order to show if these practices benefit calves in the first week of life.

The objectives of this work is to evaluate the efficacy of meloxicam, lidocaine, and both interventions given together, as compared to no pain control and a sham control, on outcomes associated with disbudding pain and inflammation in dairy calves under 5 days of age (serum cortisol, serum haptoglobin, pressure sensitivity, and laying behavior).

**Methods: Animals, interventions, assignment, and outcomes**

This work will be done on a single commercial dairy with heifer calves 1 to 5 days of age. Researchers will visit the farm two days a week at four day intervals (e.g. Mondays and Fridays). Calves will be randomly assigned to one of five treatment groups (30 calves/group, based on an expected difference in the primary outcome of pressure sensitivity of 0.5 kgf between treatment groups (1.0 vs. 1.5) with a SD of 0.5 kgf). Calves are eligible for the trial if they have health scores (McGuirk) of equal to or less than: 3 (rectal temperature), 2 (nasal discharge, ocular discharge, cough score, and feces), and 1 (ear position, naval, joint) and are not appreciably polled by palpation of the horn bud area. All interventions will be administered by the research team and all outcomes evaluated by the research team.

**Intervention groups**

(1) **PLACEBO**: Non-caustic paste, saline cornual nerve block, placebo meloxicam;

(2) **PASTE**: Caustic paste, saline cornual nerve block, placebo meloxicam;

(3) **PASTE+M**: Caustic paste, saline cornual nerve block, meloxicam;

(4) **PASTE+L**: Caustic paste, lidocaine cornual nerve block, placebo meloxicam;

(5) **PASTE+ML**: Caustic paste, lidocaine cornual nerve block, meloxicam

**Intervention allocation and blinding**

Calves will be blocked by treatment; each trial day will include all 5 treatments given to 5 calves. If more than 5 calves are born between farm visits, the first five calves examined passing the
screening protocol will be used, with a preference for a calf from each potential birth date between visits. Treatments will be assigned by shuffling five cards containing each intervention. Sequence of interventions until assigned will not be known but the research team will know that all treatments are represented in each trial replicate (day). The research team including all involved in treatment administration, data collection, evaluation, and analysis, will be blinded to the lidocaine and paste treatment by use of lettered, identical containers holding lidocaine or saline, and caustic or sham paste. Meloxicam treatments will be blinded to all involved with the exception of one research student who will know which two letter groups receive meloxicam; this person will not be involved in treatment administration, evaluation of outcomes, or analysis.

**Intervention administration**

Lidocaine or saline blocks will be administered 20 minutes prior to paste application. Hair on the horn bud will be clipped with clippers 60 minutes prior to paste, and Vaseline will be applied to control any spread of caustic paste. Calves will be observed by the research team for a minimum of four hours post-application of paste; any calves which rub paste onto other areas of their body or face will be cleaned with vinegar (which neutralizes the paste) to avoid any accidental injuries. In our experience, calves of this age are unlikely to rub the paste off of their horn buds (this is more common in older calves).

**Outcomes**

1. **Pressure sensitivity**  A pressure force algometer will be used as described by Winder et al. (2017), and readings will be taken at -60, 0, +60, +120, and +180 minutes relative to disbudding, and at the following 2 farm visits following disbudding. Sample size was based on this as the primary outcome.

2. **Serum cortisol**  18-gauge jugular catheters will be placed 60 minutes prior to paste application, and 10 mL of blood will be drawn at -20, 0, +15, +30, +45, +60, +90, +120, and +180 minutes relative to disbudding. Catheters will be flushed with a small volume of heparanized saline after each sample collection to avoid clotting. After catheter removal calves will be bandaged and monitored for a short period and the bandage material removed and all calves inspected prior to leaving the farm for the day.

3. **Haptogolbin** 10 mL of blood will be collected from the jugular catheter at -20, 0, and +180 minutes, and then on the following two visits by venipuncture from the jugular.

4. **Standing and laying behaviour**  HOBO data loggers will be used as described by Winder et al. (2017) and will be attached to calves at 60 minutes prior to paste, and will be removed at 7 days following disbudding. Data for each day will be analyzed separately, with total time spent laying, number of laying bouts, and average laying bout length offered for analysis.
Methods: Data collection, management, and analysis

The research team will be trained by CBW, and algometry readings will be taken only by two assessors who will evaluate all calves on a single trial day. Inter-observer reliability will be scored on two trial days (10 calves) by both assessors. Baseline values will be used for pressure sensitivity (-20 minutes), cortisol (-20 minutes), and haptoglobin (-20 minutes). Standing/laying behavior will not have baseline values. Recording of algometry readings, health scoring, when procedures/interventions were given to calves, when samples were taken, and any additional information such as problems with catheterization, caustic paste being smeared onto other parts of the calf, etc. will be recorded on paper by the research team and stored in a locked lab at the end of each trial day. Data will then be transferred to an excel file and checked for errors prior to cleaning. Serum samples will be held during the trial day on ice, and spun down by 6 hours post-collection. Samples for cortisol determination will be split into four samples per time point and held at – 80 C and run as a single batch in duplicate using the NCal International Standard Kit DetectX Cortisol Enzyme Immunoassay Kit with validation done by calculating sensitivity, limit of detection, and intra assay precision for the batch. Samples for haptoglobin determination will be held at –20 C and run as a single batch using the Roche Cobas 6000 c501 and biochemistry analyser with methemoglobin stock reagent using formulas and operating conditions developed by J.G. Skinner laboratory, Veterinary Investigation Centre (Aberdeen, Scotland).

Statistical analysis

Data will be exported into STATA15 (Stata/IC Version 15.1 for Mac, StatCorp, College Station, TX) and descriptive statistics reviewed for normality and variation. For algometry, cortisol, and haptoglobin, a mixed model for each outcome will be built with baseline data as a covariate and calf nested within day as a random effect. The effect of treatment on outcome will be tested, and calf age will be offered to the model. First order interaction terms between calf age, time, and treatment group will be tested. If a significant treatment by time interaction is found, single-level models will be built for each time point. For standing/laying data, daily average time spent laying and average laying bout length will be assessed as separate outcomes using a mixed model for each with calf nested within day as a random effect. Effect of treatment, calf age, and day will be tested along with first order interaction terms between these variables. If a significant treatment by time interaction if found, single-level models will be built for each day to assess the effect of treatment and calf age on outcome.

Ethics and dissemination

Ethical approval will be obtained prior to the trial start (AUP#4001). Changes to the protocol will be reported as protocol deviations in the relevant manuscript. Health data from individual calves will be communicated to the farm owner on the trial day as appropriate (i.e. for calves in need of treatment or monitoring). A summary of findings will be sent to the farm owner when
available (fall/winter 2018). Results will be analysed during the winter/spring of 2018 and should be submitted for publication by winter 2019.

References


