Protocol for a systematic review: Effects of local anesthesia and/or systemic analgesia on pain caused by cautery disbudding in calves

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Abstract

Background

Use of pain control for disbudding calves is an important welfare concern in the dairy industry, but variations in recommendations may be partially responsible for the lack of full adoption of anesthesia and analgesia by both dairy producers and veterinarians. Although narrative reviews on the use of pain control have been published, there have been no systematic reviews. This protocol describes a review of the effects of the use of local anesthesia and analgesia (using a non-steroidal anti-inflammatory drug (**NSAID**)) on the pain of cautery disbudding in calves. Cautery disbudding is currently the most commonly used method in North America of preventing horn growth, used by over three-quarters of dairy producers.

Methods

Intervention studies describing cautery disbudding in calves twelve weeks of age or younger are eligible for inclusion, provided they compare the intervention of either: local anesthesia, NSAID, or local anesthesia and NSAID, to one or more of either: local anesthesia, NSAID, or no pain control. Eligible outcomes consist of serum cortisol, pain behaviours (one or more of: ear flick, head shake, head rub, tail swish, foot stamp, or vocalization), or horn bud sensitivity (e.g. measured by algometry or von Frey monofilaments). Outcomes must be measured within the first four hours after disbudding. The search strategy will use the Agricola, Medline (via OvidSP), and Web of Science databases, as well as the Searchable Proceedings of Animal Conferences (S-PAC), ProQuest Dissertations and Theses Database, and Open Access Theses and Dissertations. If more than two studies report the same outcome at a similar time point, meta-analysis will be conducted, with subgroup analysis or meta-regression, if heterogeneity is present and an appropriate number of studies is found.

Discussion

This review will function to systematically summarize the body of evidence for the effects of local anesthesia and NSAID administration on pain caused by cautery disbudding in calves.

Keywords

Systematic review, disbudding, cautery, pain, anesthesia, analgesia, calves

Background

Pain control for the disbudding or dehorning of cattle is a key animal welfare issue in the dairy industry (Ventura et al., 2015). Although there are no systematic reviews on this topic, narrative reviews have been published (Stafford and Mellor, 2005; 2011; Stock et al. 2013). The Journal of Dairy Science has identified 'considerable variation in the recommendations' regarding pain control for these practices (Journal of Dairy Science, 2017). Perhaps accordingly, full compliance has not been achieved by either producers or veterinarians in North America with regard to the use of local anesthetic and a non-steroidal anti-inflammatory drug (**NSAID**), which is the current industry and veterinary groups' recommendation regarding pain control (Canadian Veterinary Medical Association, 2010; American Veterinary Medical Association, 2015; Dairy Farmers of Canada, 2015). Although arresting horn growth can be done by surgical amputation, cautery, or use of chemical methods, cautery disbudding remains the most commonly used method by dairy producers in North America, with 89, 70, and 77 % reporting use in the United States, Ontario, Canada, and Quebec, Canada, respectively (Vasseur et al., 2010; Adams et al., 2015; Winder et al., 2016). A systematic review examining the effects of these pain control practices for the most common method of disbudding (cautery) on pain in calves would serve as a stronger form of evidence for the effects of these practices than narrative reviews, and may help guide future requirements or regulations. It will also identify gaps in this body of literature and the degree, or lack, of homogeneity among reported interventions and outcomes, which should serve to inform future research designs and study reporting.

Methods

Study registration

This protocol is archived in the University of Guelph Library online repository and published online with Systematic Reviews for Animals and Food (**SYREAF**).

Review question

This review seeks to fully explore the effects of local anesthesia and/or NSAID on pain caused by cautery disbudding in calves. Disbudding refers to the removal or destruction of the horn bud tissue prior to attachment to the base of the skull, which occurs at approximately two months of age. Cautery disbudding is performed by use of a hot iron (typically electric or gas-powered) applied to the tissue causing a third-degree burn to effectively destroy the germinal tissue; depending on the diameter of the cautery iron, it can be used on horn buds or horns up three months of age.

Eligibility criteria

Primary study design, characteristics, and population. This review will encompass primary intervention studies available in English, including both randomized and non-randomized clinical trials. Observational study designs are not eligible for inclusion. Studies using bovine calves 12 weeks of age or less who are undergoing cautery disbudding with no concurrent painful procedures are eligible for inclusion. Concurrent painful procedures are defined as one or more of castration, branding, or any surgical procedure.

Intervention and comparator groups. Eligible studies must have included at least two of the following experimental groups: no pain control given, local anesthetic alone, NSAID alone, or local anesthetic and NSAID.

Outcome measures. Many outcomes have been used in disbudding studies as indicators of pain. For inclusion in this systematic review, studies must include one of the following outcomes, measured at one or more time points within four hours following disbudding: serum cortisol, pain behaviours (one or more of: ear flick, head shake, head rub, tail swish, foot stamp, and vocalization), or sensitivity of the horn bud (e.g. measured by an algometer or von Frey monofilaments). These outcomes were chosen based on consideration of their use in the body of literature as well as their acceptability to act as a proxy for the experience of pain.

Information sources & search strategy

Search terms are listed in table 1, with the controlled vocabulary option used where available. Electronic searches will be completed using Agricola, Medline (via OvidSP), and Web of Science databases. Grey literature will be searched to find unpublished data using Searchable Proceedings of Animal Conferences (S-PAC) as well as ProQuest Dissertations and Theses Database and Open Access Theses and Dissertations. The literature search will be conducted in April, 2017, and limited to English language publications. Search results will be uploaded to EndNoteX7™ (Clarivate Analytics; Philadelphia, PA, United States) and duplicate results documented and removed. No restriction on publication date will be placed aside from that of the database (Agricola, 1970; Medline, 1950; Web of Science, 1900; S-PAC, 1935; ProQuest, 1997; Open Access, 1990). Ten relevant studies will be pre-selected by TFD and search results will be checked to ensure these studies are included. If not, the search strategy will be modified and reported as a protocol deviation. A research librarian with the University of Guelph was consulted on the search strategy (AMV).

Study selection

Studies will be exported from EndNoteX7™ into DistillerSR® (Evidence Partners Inc.; Ottawa, ON, Canada) for two rounds of screening. A primary round will be conducted independently by CLM and CBW, assessing title and abstract for relevance using the following questions:

1.) Does the title and/or abstract describe a primary intervention study?
2.) Does the title and/or abstract describe a study involving calves disbudded by cautery?
3.) Does the title and/or abstract describe one or more of the following intervention groups: local anesthetic, NSAID, or local anesthetic and NSAID?

Studies will be excluded if both reviewers agree the study does not fulfill one or more of these descriptions. An ‘unclear’ option will also be used for all questions, with the study proceeding to full text screening if all answers are either ‘yes’ or ‘unclear’. Conflicts between inclusion and exclusion by the two reviewers will be resolved by consensus and mediated by TFD if a decision cannot be reached. Secondary screening will be conducted on the full text of remaining studies by CLM and CBW independently, using the initial three questions plus the following questions:

4.) Does the study describe one or more of the following comparator groups: local anesthetic, NSAID, or no pain control?
5.) If xylazine (or other sedative) is given, is it given to both intervention and comparator group?

6.) Does the study examine at least one of the following outcomes within the first four hours after disbudding: serum cortisol, pain behaviours (at least one of: ear flick, head shake, head rub, foot stamp, or tail swish), or horn bud sensitivity (including, but not limited to, measurements by algometer or von Frey monofilaments)

Studies will be excluded if both reviewers say "no" to one of the previous questions; conflicts will be resolved by consensus and mediated by TFD if a decision cannot be reached. Study citations and reasons for exclusion at this stage of screening will be recorded. Primary screening (questions 1-3) of title abstracts will be pilot tested independently by CLM and CBW on the first 100 studies identified by the initial search of Medline (via OvidSP) (Table 1). Full text screening (questions 4-6) will be pilot tested independently by CLM and CBW on four studies pre-selected by TFD.

Data extraction

Data from studies meeting the study selection criteria will be independently extracted by CLM and CBW, and a standardized form created for data extraction will be pre-tested on four studies pre-selected by TFD. Data extraction will be conducted by CLM and CBW independently, and discrepancies will be resolved by consensus and mediated by TFD if a decision cannot be reached.

Study level data will consist of year published and study period (date or season). Population characteristics will consist of: breed, production type, housing system, commercial or research farm, mean age, sex (male, female, or mixed group), disbudding method (including disbudding iron type), and disbudding operator (producer, veterinarian, researcher, etc.). Intervention group (including any sham control group) data will consist of, for each drug given: drug name, concentration, dose (in mg, mL, or mg/kg), technique (e.g. cornual nerve block) or route (e.g. IM, IV, SC), and timing relative to disbudding iron application.

Serum cortisol. Outcomes will be extracted as continuous measures with the mean for each treatment group and standard deviation. If this is not available, measures of association will be collected, with standard error or 95 % confidence interval, and if a statistical model is used, all additional variables included will be recorded. The number of animals in each treatment group will be collected, as well as total number of sampling time points (within the first four hours), the time points relative to disbudding, and if catheterization or venipuncture was used to obtain samples. If available, data will be extracted for each measurement time point individually. If this is not available, and area under the curve or an overall mean difference (mean per group) is reported, these data will be extracted for descriptive purposes, but not used for meta-analysis.

Pain behaviours. For all individual pain behaviours (ear flick, head shake, head rub, tail swish, foot stamp, and vocalization), outcomes will be extracted as continuous measures with mean and standard deviation values for each treatment group. If this is not available, measures of association will be collected, with standard error or 95 % confidence interval, and if a statistical model is used, all additional variables included. If data on pain behaviours are recorded for multiple time periods, the data will be extracted for each time period, up to four hours following disbudding. If pain behaviours are only available as a sum of several behaviours, these data will be extracted and the type of behaviours summed will be recorded. Data at individual time-points

are preferred; if only summed data for several time-points exists, this will be extracted but will not be used in the meta-analysis. The number of animals in each treatment group will be collected, as well as total number of observation periods (within the first four hours), the time of the observation period relative to disbudding, the length of observation periods, and if observation was done live or by video recording.

Horn bud sensitivity. Horn bud sensitivity will be extracted as continuous measures with mean and standard deviation values for each treatment group. If this is not available, measures of association will be collected with standard error or 95 % confidence interval, and if a statistical model is used, all additional variables included. If data are recorded for multiple time periods, the data will be extracted for each time period, up to four hours following disbudding. The number of animals in each treatment group will be collected, as well as total number of evaluation time points (up to four hours following disbudding), and the type of measurement (e.g. algometry, von Frey monofilaments), and measurement time relative to disbudding. Data from individual time points is preferred, but if only summed data from multiple time points is available, it will be collected but not used for meta-analysis.

Risk-of-bias assessment

Assessment of bias will be done independently by CLM and CBW, and pilot tested by CLM and CBW on the same four pre-selected studies chosen by TFD chosen for data extraction testing. Disagreements will be resolved by consensus and mediated by TFD if a decision cannot be reached. Risk of bias will be assessed using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials (Higgins et al., 2011), modified by also including an assessment of reporting of randomization (in addition to random sequence generation). Risk of bias will be assessed for each outcome class (serum cortisol, pain behaviours (as a group) and horn bud sensitivity), and reported alongside the forest plot (if meta-analysis is conducted).

Data synthesis

If more than two studies report the same outcome at a similar time point and/or period utilizing the same comparison groups, meta-analysis will be conducted. 'Similar time points' are pre-defined as not more than ten minutes' difference during the first seventy minutes after disbudding, and within twenty minutes after this time. 'Similar time period' applies to pain behaviour observation windows, the larger of which is no more than 150 % of the smaller window. Time points or periods with greater differences than described above will be considered different outcomes. If more than one outcome measure was reported within a similar time period for a single study, the time point closest to the mid-point of the similar time period will be used for the meta-analysis. This will ensure that observations within a similar time period are independent. For outcomes that are measured on the same continuous scale, mean differences will be used. If different scales are used (e.g. ear flicks per 10 minutes and ear flicks per 15 minutes), mean differences will be divided by standard deviation to generate a standardized mean difference. Meta-analysis will use a random effects approach, and weighting of primary studies will done using the inverse variance method. Heterogeneity between studies will be assessed with the Q-test and I^2 statistic. Heterogeneity will be explored via sub-group analysis and/or meta-regression, if enough studies are found for a single outcome. A sub-group analysis is planned for those with and without the use of xylazine sedation for each intervention comparator group (if there are at least three studies in each group). For treatment group

comparisons of outcomes lacking at least two studies, data will be reported as a narrative synthesis.

Presentation of results
Details of the study populations, intervention groups, and outcomes assessed will be presented in a summary table. If meta-analyses are possible, results will be presented by intervention comparison group (local anesthetic v. no pain control; NSAID v. no pain control; local anesthetic and NSAID v. no pain control; local anesthetic and NSAID v. local anesthetic; local anesthetic and NSAID v. NSAID) with a summary effect measure and forest plot. Results from each study will be summarized using GRADE guidelines (Guyatt et al., 2011) assessing indirectness, imprecision, risk of bias, inconsistency, and risk of publication bias, by intervention comparison group, with absolute risk at baseline garnered from the median risk in the control groups (no pain control given) in all studies included in the meta-analysis.

Risk of bias at the review level
If ten or more studies are found for a single outcome, a funnel plot (effect estimate by inverse of standard error) will be used to visually assess potential for publication bias.

Discussion
This review will function to systematically summarize the body of evidence for the effects of local anesthesia and NSAID administration on pain caused by cautery disbudding in calves.

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References
Adams, A.E., J.E. Lombard, C.S. Shivley, N.J. Urie, I.N. Roman-Muniz, C.P. Fossler, C.A. Kopral. 2015. **Management practices that may impact dairy heifer welfare on U.S. dairy operations.** Page 105 of the Proc. of the Joint Annual Meeting of the American Dairy Science Association and American Society for Animal Science, Orlando, FL.

American Veterinary Medical Association. 2014. **Literature review on the welfare implications of the dehorning and disbudding of cattle.** Accessed March 29, 2017. https://www.avma.org/KB/Resources/LiteratureReviews/Pages/Welfare-Implications-of-Dehorning-and-Disbudding-Cattle.aspx

Canadian Veterinary Medical Association. 2010. **Disbudding and dehorning of cattle – position statement.** Accessed March 29, 2017. http://www.canadianveterinarians.net/documents/disbudding-and-dehorning-of-cattle

Dairy Farmers of Canada. 2015. **proAction: Leading the way for sustainable dairy farming; providing assurance to customers about farm practices.** Dairy Farmers of Canada, Ottawa, Ontario, Canada. Accessed March 29, 2017. https://www.dairyfarmers.ca/Media/Files/proaction/proaction_ang_lr15.pdf

Guyatt, G., A.D. Oxman, E.A. Akl, R. Kunz, G. Vist, J. Brozek, S. Norris, Y. Falck-Ytter, P. Glasziou, H. deBeer, R. Jaeschke, D. Rind, J. Meerpohl, P. Dahm, H.J. Schunemann. 2011. **GRADE guidelines: 1. Introduction – GRADE evidence profiles and summary of findings tables.** J. Clin. Epi. 64:383-394.

Higgins, P.T., D.G. Altman, P.C. Gotzsch, P. Juni, D. Moher, A.D. Oxman, J.A.C. Sterne. 2011. **The Cochrane Collaboration's tool for assessing risk of bias in randomized trials.** BMJ 343:d5928 doi: 10.1136/bmj.d5928

Journal of Dairy Science. 2017. **JDS Collections: Disbudding and pain management for calves.** Accessed March 29, 2017. http://www.journalofdairyscience.org/content/disbudding

Stafford, K.J., and D.J. Mellor. 2005. **Dehorning and disbudding distress and its alleviation in calves.** Vet. J. 169: 337-349.

Stafford, K. J., and D. J. Mellor. 2011. **Addressing the pain associated with disbudding and dehorning in cattle.** Appl. Anim. Behav. Sci.135:226–231.

Stock, M. L., S. L. Baldridge, D. Griffin, and J. F. Coetzee. 2013. **Bovine dehorning: Assessing pain and providing analgesic management.** Vet Clin. North Am. Food Anim. Pract. 29:103–133.

Vasseur, E., F. Borderas, R. I. Cue, D. Lefebvre, D. Pellerin, J. Rushen, K. M. Wade, and A. M. de Passille. 2010. **A survey of dairy calf management practices in Canada that affect animal welfare.** J. Dairy Sci. 93:1307-1315.
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Ventura, B. A., M. A. G. von Keyserlingk, and D. M. Weary. 2015. **Animal welfare concerns and values of stakeholders within the dairy industry.** J. Agric. Environ. Ethics 28:109–126.

Winder, C.B., S.J. LeBlanc, D.B. Haley, K.D. Lissemore, M.A. Godkin, T.F. Duffield. 2016. **Practices for the disbudding and dehorning of diary calves by veterinarians and dairy producers in Ontario, Canada.** J. Dairy Sci. 99:1-13.

Table 1. Initial search strategy conducted in Medline (via OvidSP) on 03/22/17.

#	**Search terms**	**Results**
1	calf OR calves OR cattle OR bovine OR dairy OR beef OR Holstein OR Friesian OR Jersey OR ruminant	467 438
2	disbud* OR dehorn* OR cautery OR electric OR rhinehart OR rhinehardt OR iron OR portasol OR express OR buddex OR propane OR butane OR torch	611 226
3	**1** and **2**	12 853
4	freezing OR numbing OR local OR anesthetic OR anaesthetic OR lidocaine OR block OR bupivacaine OR lignocaine OR NSAID OR metacam OR meloxicam OR flunixin OR banamine OR ketoprofen OR anafen OR non-steroidal anti-inflammatory OR anti-inflammatory OR analgesia OR pain control OR pain mitigation OR meclofenamic acid OR phenylbutasone OR bute OR carprofen OR salicylic acid OR ASA OR aspirin OR naproxen OR tolfenamic acid OR metamizaole sodium	1 277 043
5	**3** and **4**	666