Title:

Efficacy of pain management for cattle castration: a protocol for a systematic review and a meta-analysis

Registration:

Protocol for this systematic review was prepared following PRISMA-P guidelines (Moher et al., 2015). This protocol is deposited in the University of British Columbia's digital repository (cIRcle) available at: https://open.library.ubc.ca/ and registered with the Systematic Reviews for Animals and Food (SYREAF), available at: http://www.syreaf.org/contact/.

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Contributions:

JS will act as review leader, hence will be responsible for coordinating the review, preparing a protocol, preforming primary and secondary screening, data extraction, risk of bias assessment, and the meta-analysis. All drafts of the protocol and the final manuscript will be prepared by JS with input from MAGvK, DMW, BJS and EN. BJS will provide methodological expertise and assist in the statistical analysis. EN will be involved in primary and secondary screening, data extraction and risk of bias assessment. All authors will read and approve the final version of the review.

Amendments

Deviations from this protocol that will occur during the review process will be reported as protocol deviation in the final manuscript accompanied with a rational for the changes.

Support

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Introduction

Rational

The majority of male calves are castrated using one of three methods (Stafford and Mellor, 2005): surgical (i.e., orchidectomy), crushing the tissue at the scrotal neck with a Burdizzo clamp, and rubber ring (applying continuous pressure at the scrotal neck interrupting blood flow). Over the past three decades much research has attempted to compare these castration methods and evaluate the associated pain (reviewed by Coetzee, 2011). Generally, there is a strong agreement within the literature that all castration methods are painful (Stafford et al., 2002; Stafford and Mellor, 2005; Coetzee, 2011), but there is little consensus on the efficacy of pain control strategies and how this varies with castration method.

A recent narrative review suggested that the effect of unimodal analgesia (local anesthetic alone) is less effective than multimodal methods (providing a combination of local anaesthetic and NSAID; Coetzee, 2011), but to our knowledge there has been no systematic review or meta-analyses of the available literature on pain management for cattle castration.

Objectives

The primary objective of this review is to evaluate the effect of unimodal and multimodal analgesia during cattle castration, on outcome measures thought to be pain related and frequently reported in this literature. This will include plasma or saliva cortisol, average daily gain (ADG), and pain behaviors (i.e., foot stomping, wound licking, visual analog scale (VAS), stride length). The results will be considered and analyzed separately by castration method (specifically comparing surgery, Burdizzo clamp or rubber ring). Results will be presented descriptively, and in cases where sufficient studies using similar methods reported similar outcomes, meta-analyses will be completed and results presented. We will also identify gaps in the literature including inconsistencies in methods and in outcome measures reported.

Research question:

What is the efficacy of pain treatments strategies applied during cattle castration on alleviating pain related outcome measures?

a. Population: Bovine calves and young stock subjected to castration
b. Intervention: Application of pain treatment (i.e., local anesthetic, NSAID)
c. Comparator: Different pain treatments. **Primary research interest** is to assess the efficacy of the multimodal analgesia (local anesthetic and NSAID) by comparing to the control group without any pain medication. **Secondary research interest** is to assess the efficacy of unimodal analgesia (local anesthetic) by comparing to the

control group without any pain medication. Additional **exploratory research** will compare the two treatments multimodal versus unimodal analgesia.

d. Outcomes:
   - Plasma or saliva cortisol in the first 24 h after castration, compared hourly. Time points for comparison will be chosen depending on the pharmacodynamics of the treatment (possibly at 1 h, 4 h, 6 h, 12 h and 24 h; prioritization of time points may be applied depending on treatment)
   - ADG in the first 4-8 weeks after castration, compared weekly (prioritization of time points may be applied depending on treatment)
   - Pain behaviors (foot stomping, wound licking, VAS, stride length) in the first 4-8 weeks after castration, compared at least two time points, in the first 24 h and weekly thereafter (prioritization of time points may be applied depending on treatment)

Methods

Eligibility criteria

Studies will be selected based on the criteria described below.

Population Characteristics and Study Design

Studies will be eligible if they included bovine calves and young stock that underwent only castration (surgical, rubber ring or Burdizzo clamp), with no other concurrent painful procedures. Only experimental intervention studies, randomised and not randomised, will be eligible for inclusion (observational studies will not be included).

Intervention and Comparator Group

Studies will be eligible if they provided within castration method comparisons and included at least two of the following comparison groups: control group, where pain was not mitigated, and a group where pain was alleviated using local anesthetic alone, or an NSAID alone, or combination of local anesthetic and NSAID.

Outcome Measures

Studies will be eligible if they reported at least one pain related measures including: plasma cortisol, saliva cortisol, average daily gain (ADG) or pain behaviors (i.e., foot stomping, wound licking, visual analog scale (VAS), stride length). Both plasma and saliva cortisol measures have to be recorded (and reported) at least once or several times within 24 h following the castration procedure. Pain behaviors have to be recorded at least once or several times within the 6 weeks after the procedure, while ADG have to be reported at least once within the 6 weeks after castration.

Language

We will include literature published in the English language only.

Other inclusion criteria

Peer reviewed articles, and gray literature such as conference proceedings and thesis must: (1) be publicly available, (2) provide detailed explanation of the experimental design, and (3) provide measures of variation (e.g., SD), to be included in this review. Conference proceedings and

thesis chapters that were found published in peer reviewed journals will be considered as duplicates and removed.

Information Sources

We will search Web of Science (https://apps.webofknowledge.com), Agricola using the Agricultural & Environmental Science Database (https://search-proquest-com.ezproxy.library.ubc.ca/agricenvironm/), and Medline (Ovid; http://ovidsp.dc2.ovid.com) for relevant literature, including peer reviewed articles and conference proceedings, from Jun 22 to June 30, 2020. Additionally, unpublished literature such as doctoral and master thesis will be searched using the ProQuest Dissertations and Thesis Database (https://search.proquest.com/databases/). The search will be limited to literature published in the English language, but not restricted by publication date.

Search strategy

The research team consulted with a librarian (K. Miller) from the University of British Columbia to develop the following search: (calf OR calves OR bull* OR cattle OR bovine) AND (castration OR "surgical castration" OR burdizzo OR "clamp castration" OR band* OR "rubber ring castration") AND (anesthetic OR *caine OR NSAID OR metacam OR meloxicam OR flunixin OR banamine OR ketoprofen OR anafen OR non-steroidal OR anti-inflammatory OR analgesia OR "pain control" OR "pain mitigation" OR phenylbutasone OR carprofen OR "salicylic acid" OR aspirin).

Study records

Data management

The results from the literature search from all databases will be downloaded to a bibliographical management software EndNote (Philadelphia, PA, USA). Records from EndNote will than be uploaded into a systematic review software Covidence (Melbourne, Australia). Duplicates will be removed before starting the screening process. The screening process will be piloted by the reviewers using a subset of 20 studies, and improved if needed.

Selection process

Studies identified by this search will be subjected to a 2-step screening process, using the Covidence software tools. This process will be completed independently by two researchers (JS and EN), and any disagreement will be resolved through discussion, with mediation if required by DMW. Initially titles and abstracts will be screened using the inclusion and exclusion criteria described above. Specifically, the title and abstract will be selected if they are: (1) available in English language, (2) describe an intervention study related to castration in cattle and (3) contain use of pain mitigation such as local anaesthetic, NSAID or both. Also, studies have to report at least one of the outcome measures of interest: plasma cortisol, saliva cortisol, ADG or one of the pain behaviors of interest. Records will be excluded for further screening if both reviewers answer 'no' to any of the listed criteria. In cases when both reviewers answered 'yes' or 'maybe' for all criteria, records will be retained for further full text screening. Remaining records will undergo the second step of screening, which will include application of the abovementioned criteria by two independent reviewers on the full text. Reasons for exclusion of studies during the review process will be recorded and later compared between the two reviewers. The reference lists of the retained papers will be also screened to identify additional papers. Records that passed the second full text screening step will be used for data collection.

Data Collection Process

Data from selected eligible studies will be extracted independently by the two reviewers (JS and EN) using data extraction form created using the Covidence software. The extraction form will be piloted and tested by the reviewers preforming the data extraction using a subset of 20 studies, and improved if needed. Inconsistencies in data extraction will be solved through discussion and mediated by DMW when needed. Data reported graphically will be extracted using WebPlotDigitizer (version 4.2). Authors will be contacted via email in cases when the data are unextractable, unclear or missing. Authors will be provided 2 weeks to respond with one follow up reminder 7 days following the initial email.

Data items

Tables summarizing findings from individual studies will be extracted using the Covidence tools and will include the following: first author and publication year, country of origin, population characteristics (breed and age), number of animals used, castration method, treatment including drug name, dosage, route and application time, relative to castration.

Outcomes and prioritization

Primary outcomes

Plasma and saliva cortisol. Data for plasma and saliva cortisol at different sampling time points following castration will be extracted as mean and standard deviation for each treatment group, including the number of subjects per group. Otherwise, estimates of associations with standard error or 95% confidence intervals were used. Data for individual time points will be extracted and used for comparison in the meta-analyses. When cortisol is reported as area under the curve (AUC), it will be used for descriptive purposes only.

Secondary outcomes

Average daily gain (ADG). Data on ADG will be gathered for each treatment group, including the number of subjects per group. Mean and standard deviation for ADG at different time points following castration will be extracted and used for the meta-analysis. If not available, estimates of associations with standard error or 95% confidence intervals will be used. Data for individual time points will be extracted and used for comparison in the meta-analyses. When ADG is reported only as a summary for the entire study, it will be used for descriptive purposes only.

Pain behaviors. Data for foot stomping, wound licking, visual analog scale (VAS) and stride length, at different sampling points following castration will be extracted as means and standard deviation, including the number of animals in each intervention group. If these descriptors are not available, estimates of associations with standard error or 95% confidence intervals will be used. Studies have to report that quality control was implemented (i.e., within and/or between observer reliability tests) when behavioral measures were gathered to be included in this review. When quality control was achieved, but measures were reported as a summary for several time points instead of individual time points, behavioral measures will be reported descriptively.

Risk of Bias in Individual Studies

Risk of bias will be completed by 2 reviewers independently and performed for each outcome measure using the revised Cochrane risk-of-bias tool for randomised trials (RoB 2; Higgins et al., 2016). The signaling questions outlined in this tool will be modified where necessary. Full

description of the RoB 2 tool is available at https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool.

Data Synthesis

Meta-analysis will be performed if the same outcome measure is reported at similar time points in more than 2 studies. For plasma or saliva cortisol, time points will be considered similar (and comparable) if there is no more than ±15 min difference between the time points in the first 3 h and no more than ±30 min difference in the following period. Average daily gain has to be reported as 7 d or weekly summary to be considered for analysis. Pain behaviors will be considered similar (and comparable) if there is no more than ±15 min difference between the time points during the first 24 hours after castration. Daily summary or daily assessments of pain behaviors will be used thereafter.

Meta-analysis will be completed in RStudio using random effect model for continuous outcome with each study being weighted by inverse of their variance. Between study variance, i.e., heterogeneity will be estimated using DerSimonian-Laird estimator, accompanied by the appropriate 95% confidence interval. In addition, heterogeneity will be estimated using I^2 accompanied by its 95% confidence interval; Q test will also assess statistical significance of the heterogeneity.

Presentation of results

Summary of the study population, treatment groups and outcome measures will be provided in tables. If meta-analyses are completed comparison of treatment groups of interest will be illustrated using forest plots.

Meta-bias(es) (publication bias across studies, selective reporting within studies)

Graphical assessment of funnel plot symmetry will be used to assess the potential publication bias.

Confidence in cumulative estimate

References

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