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STUDY REVIEW

Systematic Review: Analgesia for Calf Disbudding

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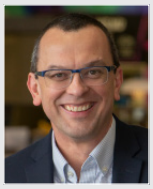

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Jon Huxley was raised on the family dairy farm in North Wales and graduated from the Royal Veterinary College, London in 1995. Following 4 years in farm animal practice, he completed a PhD on bovine mastitis at the University of Bristol. He remained at Bristol as a Lecturer until 2006 when he became a foundation staff member at the University of Nottingham's new Veterinary School. In May 2018 he moved to Massey University, to become Head of the School of Veterinary Science and Professor of Dairy Cow Health. Jon is a research clinician specialising in the endemic diseases of dairy cows, particularly the impacts of production and the environment on dairy cow health and wellbeing.

Winder CB, et al. Effects of local anesthetic or systemic analgesia on pain associated with cautery disbudding in calves: A systematic review and meta-analysis. J Dairy Sci. 2018;101(6):5411–5427

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This Study Review summarises and critically evaluates the systematic literature review conducted by Winder et al. that examined the use of local anaesthesia and NSAID analgesia in pain management for calf disbudding. This article is supported by an educational grant by Boehringer Ingelheim.

Background

Disbudding of calves is a common procedure in beef and dairy production.[1] There are three primary methods of disbudding cattle: amputation using scoop dehorners; cautery using a hot iron; and chemical application of caustic paste. Irrespective of the technique used, behavioural and physiological responses indicate that the removal of horn buds is a painful procedure and not addressing the issue of pain associated with disbudding becomes a calf welfare issue.[1,2]

Indeed, Regulations 57 and 58 of the Animal Welfare (Care and Procedures) Regulations 2018 require local anaesthesia to be used for disbudding or dehorning,[3] and the New Zealand Veterinary Association recommends that a combination of local anaesthetic, NSAID, and sedation should be considered to manage the pain associated with disbudding.[4]

Rationale and objectives

The aim of the systematic review was to examine the effects of local anaesthesia or NSAID analgesia on pain control in calves following cautery disbudding.[5] Meta-analyses were performed if a sufficient number of included studies reported a specific outcome at a similar time point, otherwise the synthesis was qualitative.

Gaps between primary research and the application of policy in the dairy industry may be due, at least in part, to a lack of consistent recommendations emanating from primary research studies.[5] Systematic reviews serve as a stronger form of evidence for the effects of a clinical intervention than the results of a single research study or narrative review. Of particular note, narrative reviews do not include evidence-based methods to identify, analyse, and synthesise data, leading to conclusions that are susceptible to bias. Appropriately conducted systematic reviews offer a more robust and transparent methodology to identify, evaluate, and summarise evidence to answer a specific clinical or policy question.[6]

Methodology

The protocol for this systematic review was developed according to PRISMA-P 2015 guidelines.

Eligibility criteria

- **Study design:** Randomised and non-randomised clinical trials available in English were eligible for inclusion.
- **Study population:** Calves aged ≤12 weeks who underwent cautery disbudding with no concurrent painful procedures (castration, branding, and/or any surgical procedure).
- **Treatments:** Eligible studies must have included ≥2 of the following experimental groups: no pain control given; local anaesthetic alone; NSAID alone; or local anaesthetic and NSAID.

Outcome measures

One or more of the following outcomes (measured at ≥1 time point): plasma cortisol levels; pain behaviours (≥1 of ear flick, head shake, head rub, tail swish, foot stamp, and vocalisation); or pressure tolerance (i.e., sensitivity) of the horn bud (measured using either an algometer or Von Frey monofilaments).

Information sources

Electronic searches were completed using Agricola, Medline, and Web of Science databases. Grey literature was searched to find unpublished data using Searchable Proceedings of Animal Conferences as well as ProQuest Dissertations and Theses Database and Open Access Theses and Dissertations.

Study selection

Studies went through two rounds of screening. The first round was conducted independently by two of the authors assessing title and abstract for relevance based on three questions. Studies were excluded if both reviewers agreed that the study did not fulfil ≥1 of these criteria. Conflicts between inclusion and exclusion by the two reviewers were resolved by consensus.

The second round of screening was conducted independently by two of the authors assessing the full text of the remaining studies based on the initial three questions and a set of three more questions. Studies were excluded if both reviewers said no to one of the second set of questions, with conflicts being resolved by consensus.

Data extraction

Data from studies meeting the study selection criteria were independently extracted by two of the authors using a standardised form, which was pre-tested on four studies pre-selected by one of the authors. Discrepancies in data extraction were resolved by consensus.

Outcomes data were extracted as a continuous measure with mean and standard deviation values for each treatment group.

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Risk of bias in studies

Assessment of the risk of bias in individual studies was performed independently by two of the authors and was pilot tested by two of the authors on the same four pre-selected studies chosen for data extraction testing. Disagreements were resolved by consensus.

Risk of bias was assessed using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials,[7] which was modified by the additional inclusion of an assessment of reporting of randomisation.

Synthesis of study results

Meta-analysis was performed if >2 studies reported the same outcome at a similar time point or period with the same comparison groups. Heterogeneity between studies was assessed with the I^2 statistic.[8] Heterogeneity was assessed via subgroup analysis or meta-regression if there were enough studies for a single outcome.

Expert comment: Systematic reviews with meta-analyses are considered one of the highest quality forms of evidence, as they allow the impartial synthesis of all the available scientific evidence on a subject. The authors have followed an appropriate set of reporting guidelines (the PRISMA statement) designed to reduce the chance of introducing bias and to allow a full, clear, and transparent report of their approach. Within that framework, the approach the authors have taken, including their selection criteria, outcome parameters, and bias risk analysis, appear sound. As a final note, the article is published in one of the highest-ranking journals in the field and is from a group with a long and distinguished track record of excellence in the fields of cattle health and evidence-based medicine. Whilst of course neither of those things preclude this being a poorly conducted review, they are indicators that can give the inexperienced reader more confidence.

Results

A total of 75 full-text articles were reviewed of which 54 did not meet eligibility criteria; hence, 21 articles, involving 23 separate experiments, were included in the qualitative synthesis (**Figure 1**).

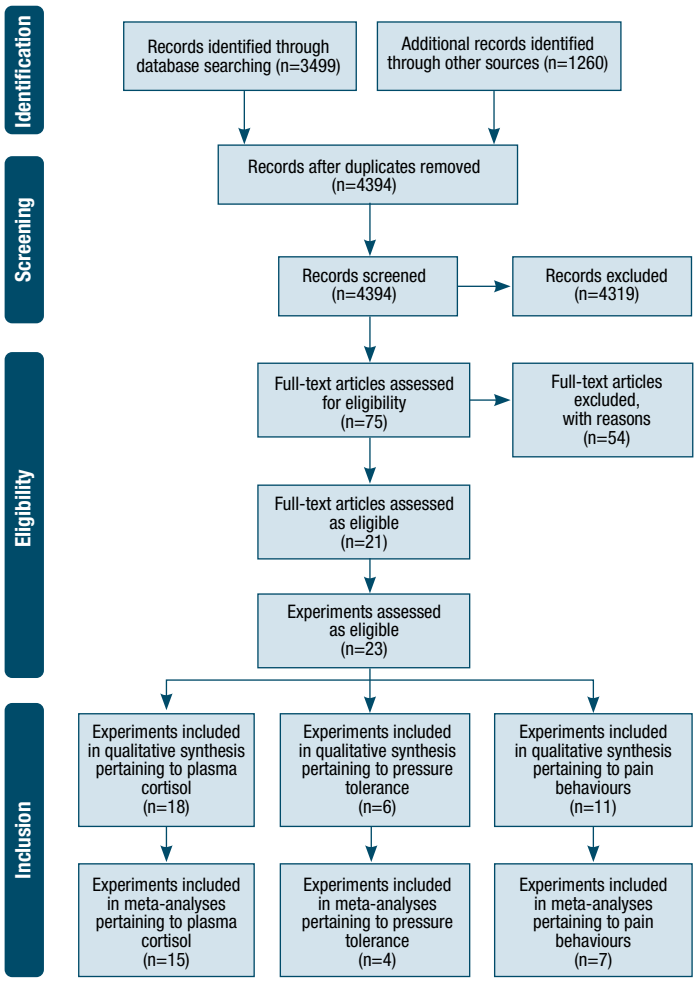

Figure 1. Study flow diagram: Results of the search strategy and study selection.

Interventions and comparator groups

Of the 21 included studies, 12 contained an intervention group receiving local anaesthetic with a comparator of saline or no treatment and 17 trials compared a local anaesthetic and NSAID with anaesthetic alone. The specific NSAIDs assessed were: carprofen; dexketoprofen; firocoxib; flunixin meglumine; ketoprofen; and meloxicam (**Table 1**).

NSAID	Studies	Routes of administration	Doses	Times of administration
Carprofen	N=4	IV, oral, and SC	1.4 and 2.0 mg/kg	5, 10, and 15min pre-disbudding
Dexketoprofen	N=1	IV	3.0 mg/kg	30min pre-disbudding
Firocoxib	N=2	Oral	0.5 and 2.0 mg/kg	5 and 10min pre-disbudding
Flunixin meglumine	N=2	IV	2.2 and 2.3 mg/kg	At disbudding and 3hrs post-disbudding
Ketoprofen	N=3	IM and oral	3 mg/kg	10min and 2hrs pre-disbudding, and 2 and 7hrs post-disbudding
Meloxicam	N=5	IM, IV, and oral	0.5, 1.0, and 3.0 mg/kg	At disbudding, and 5, 10, and 55 min pre-disbudding

Table 1. NSAID protocols in the 17 treatment trials comparing local anaesthetic and NSAID with local anaesthetic alone that were included in the systematic review.
Abbreviations: IM = intramuscular; IV = intravenous; SC = subcutaneous.

Synthesis of study results by outcome

Plasma cortisol

Of 18 studies that reported measuring plasma cortisol levels, 15 were included in meta-analyses (**Figure 1**). Comparisons of local anaesthesia versus control and local anaesthesia plus an NSAID versus local anaesthesia alone were assessed.

Administration of local anaesthetic alone was associated with significantly reduced plasma cortisol levels until 2hrs post-disbudding, although there was considerable heterogeneity between studies (I^2>50%) [**Figure 2A**]. This was followed by a rise in cortisol peaking at 4hrs post-disbudding, with substantial heterogeneity (I^2>50%). No effect of local anaesthetic on cortisol was evident at 6 and 24hrs and substantial heterogeneity was again present (I^2>50%). The addition of an NSAID to local anaesthetic resulted in a significant reduction in plasma cortisol levels at 4hrs, with moderate heterogeneity between studies (I^2=46%) [**Figure 2B**]. At 24hrs, plasma cortisol levels were significantly greater in calves that received local anaesthesia and NSAID, with moderate heterogeneity (I^2=46%) being noted.

Pressure tolerance

Of the six studies identified that reported measuring pressure tolerance, four were included in the meta-analysis (**Figure 1**). Only comparisons of local anaesthesia plus NSAID with local anaesthesia alone were assessed.

No effect of treatment on pressure tolerance was seen at 2hrs post-disbudding, with moderate heterogeneity present between studies (I^2=37%), but at 4 or 6hrs post-disbudding an overall effect of local anaesthesia and NSAIDs relative to local anaesthesia was seen with calves tolerating more pressure on the areas around their horn bud, with no heterogeneity between studies present (I^2=0%) [**Figure 3**]. For all further time points (8, 12, 24, 48, 72, or 96hrs), no effect of treatment was observed, with low heterogeneity between studies (I^2=0–20).

Pain behaviour

Seven of 11 studies reporting measuring ≥1 pain-related behaviour were included in the meta-analyses (**Figure 1**). Only comparisons of local anaesthesia plus an NSAID with local anaesthesia alone were assessed.

No treatment effect on ear flicks was seen at 1hr, although there was substantial heterogeneity between studies (I^2=90%) [**Figure 4A**]. A protective effect of local anaesthesia and NSAIDs relative to local anaesthesia was seen at 3 and 4hrs, with low heterogeneity (I^2=22% and 0%, respectively). For subsequent times, no overall effect of treatment on ear flicks was observed, although substantial heterogeneity was present between studies (I^2>50%).

No effect of treatment was seen on head shake at 1hr post-disbudding and there was no heterogeneity present between studies (I^2=0%) [**Figure 4B**]. However, a protective effect of local anaesthesia and NSAIDs relative to local anaesthesia was found at 4 or 6 hrs post-disbudding, also with no heterogeneity between studies (I^2=0%). At 24hrs post-disbudding, no overall treatment effect on head shake was seen, with substantial heterogeneity between studies (I^2= 59%).

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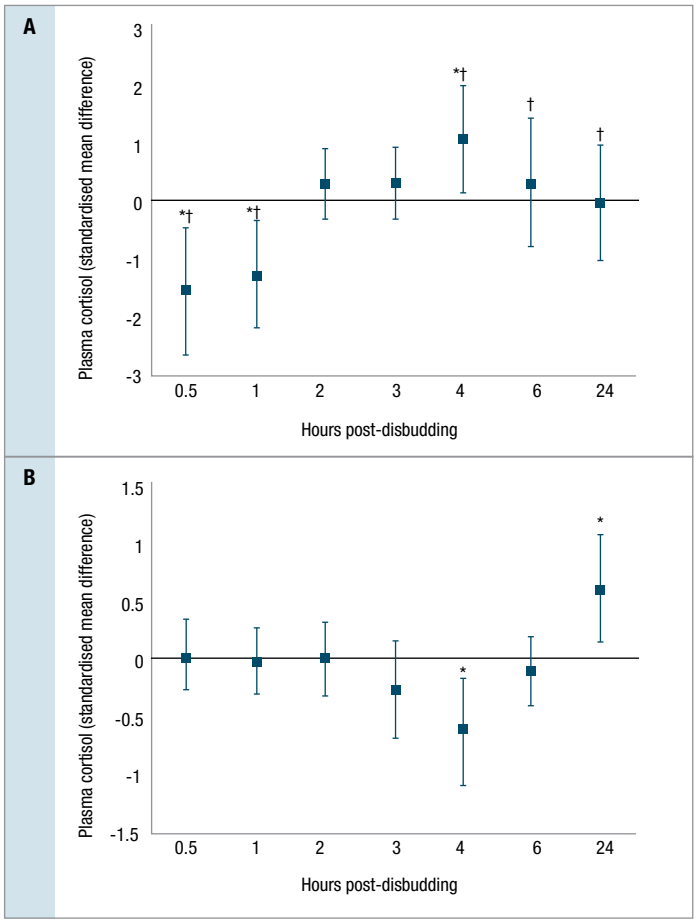

Figure 2. Forest plots for plasma cortisol level outcomes: Overall effect measures (±95% CI) of random effects meta-analyses of the effect of (**A**) local aesthesia versus with control on standardised mean difference in plasma cortisol and (**B**) local anaesthesia and NSAID versus local anaesthesia on standardised mean difference in plasma cortisol. * Significant overall effect of treatment p<0.05; † Substantial heterogeneity (I^2>50%).

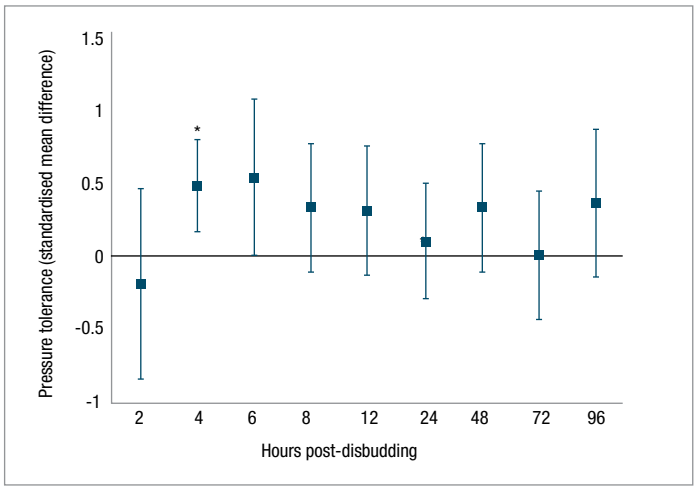

Figure 3. Forest plot for pressure tolerance outcome: Overall effect measures (±95% CI) of random effects meta-analyses of the effect of local anaesthesia and NSAIDs compared with local anaesthesia alone on standardised mean difference in horn bud pressure tolerance (sensitivity). * Significant overall effect of treatment (p<0.05).

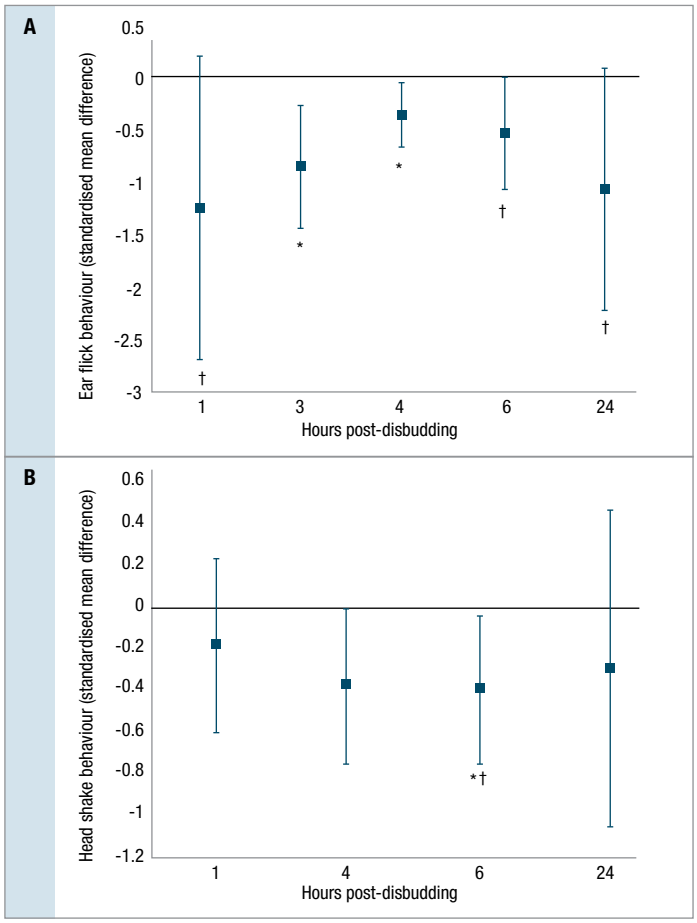

Figure 4. Forest plots for pain behaviour outcomes: Overall effect measures (±95% CI) of random effects meta-analyses of the effect of local anaesthesia and NSAID compared with local anaesthesia on standardised mean difference in (**A**) ear flick and (**B**) head shake behaviour. * Significant overall effect of treatment p<0.05; † Substantial heterogeneity (I^2>50%).

Outcomes summary

When plasma cortisol levels are used as an indicator of stress and pain, cortisol increases rapidly following disbudding, peaking within the first 30 minutes.[1] Typically, the levels then plateau for 1–6hrs before declining and returning to baseline 7–8hrs following disbudding.

In the meta-analysis, the addition of an NSAID to local anaesthetic resulted in reductions plasma cortisol levels at 4hrs and in pressure tolerance and pain behaviours (in some analyses) between 3 and 6hrs post-disbudding.[5] The beneficial effects occurring at 3, 4, and 6hrs post-disbudding when NSAID was given in addition to local anaesthetic likely corresponds to the time after the duration of action of the local anaesthetic and may be due to a reduction in the inflammatory pain response.

Overall, a protective effect of local anaesthetic was seen for the acute pain of cautery disbudding with the subsequent delayed rise in cortisol being mitigated by the addition of an NSAID, which also reduced other signs of pain, including pressure tolerance and pain behaviours.[5]

Expert comment: Overall, the results support the use of NSAID in addition to local anaesthetic when calves are disbudded by hot iron cautery. Systematic reviews with meta-analysis are abundant in the human medical literature and are the cornerstone of high-quality evidence-based medicine policy. They remain relatively uncommon in the veterinary literature, in part because they rely on an adequate number of primary research studies to appraise. We are fortunate that this is one area where enough studies exist; however, in order to amalgamate the data, the authors have had to include a range of differing methodological approaches (e.g., NSAID, dose rate, route of administration, outcome measure, etc). This heterogeneity of approach is reflected in the heterogeneity of the results. Similarly, the authors have had to include studies that are less than adequately conducted and/or reported, which increases the risk of bias (incidentally, the increased use of reporting guidelines in the veterinary literature should reduce this problem in the future). The authors identify both of these issues and handle them appropriately and in an open and transparent manner.

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Discussion

The authors of the systematic review concluded that the use of a local anaesthetic plus an NSAID is best practice for mitigation of pain following cautery disbudding of calves.[5] This conclusion is supported by three non-systematic literature reviews of analgesia for cautery disbudding of calves that also identified advantages of adding a systemic NSAID to a local anaesthetic following disbudding in terms of pain management.[1,2,9]

Considerable variability in the studies included in the systematic review, i.e., six different NSAIDs given via four different routes, sometimes at different dosages, and at a range of administration time points (**Table 1**), prevented a subgroup analysis being undertaken to identify differences among the NSAIDs.

The heterogeneity was likely largely due to differences in pharmacological properties among the different NSAIDs. For example, the elimination half-lives of meloxicam (21.9hrs[10]) and carprofen (30–40hrs[11]) are longer than those of ketoprofen (0.42hrs[12]), salicylate (0.5hrs[13]), and flunixin meglumine (4–8hrs[14]), which suggests that meloxicam and carprofen have a longer duration of action than other NSAIDs used in cattle.[10] Duration of analgesic effect is relevant because after an initial acute pain response (≤30min after disbudding) there is evidence of inflammatory pain lasting ≤8hrs and increased sensitivity possibly lasting for ≤72 hours post-disbudding.[9,15] NSAIDs with a shorter elimination half-life require repeated administrations to sustain therapeutic levels.[1]

Of the three outcomes assessed in the systematic review, pain behaviour was the most difficult to synthesise primarily due to between-study differences in study design and duration of observation period as well as data extraction complications.[5] Additionally, pain behavioural responses are subject to interpretation and reliable indicators of pain are difficult to assess in cattle following disbudding with and without analgesia.[1] Although the findings of the review indicated that a protective effect of NSAID use on pain behaviour exists, difficulties in combining studies prevented estimation of the exact nature of the effect and duration of NSAID use on pain behaviour.[5]

The analysis produced some apparently aberrant cortisol level results at several time points, specifically treatment with local anaesthesia resulting in higher cortisol levels than saline or no treatment at 4hrs post-disbudding, a protective effect of no treatment on plasma cortisol levels at 24hrs post disbudding, and local anaesthesia plus NSAID resulting in higher cortisol levels relative to local anaesthesia alone at 24hrs post disbudding.[5] These results were associated with moderate to substantial heterogeneity among studies. Study heterogeneity indicates inconsistency of effect between studies, which could be due to a range of factors including random variation, methodological variation, and small sample. In addition, factors other than the use of pain control may have affected plasma cortisol levels including differences in handling methods, timing of sample collection, and diameter of disbudding iron and hence the resultant wound size. Factors associated specifically with pain control, such as percentage of active ingredient, volume used, technique used, and whether epinephrine was included, could also have influenced plasma cortisol levels.

Assessing the risk of bias in the relevant research studies is an important consideration in systematic reviews.[16] The risk of bias of the studies included in the systematic review was independently assessed by the authors using a modified Cochrane Collaboration's tool for assessing risk of bias in randomised trials.[5] The authors reported that the assessment of study bias risk was problematic due to important information often being unreported. Twelve of 17 studies did not report the method of randomisation to treatment and the method of blinding was reported in only one study. Not reporting key design features can result in biased effect estimates.[17]

Expert comment: I agree with the authors' conclusions. Where inadequacies in their work exist they are predominantly down to the quality of and limitation in the available literature, rather than the approach the authors have taken or how they have reported their findings. Based on their work, I believe we can be as sure as the current evidence allows that the use of a local anaesthetic plus an NSAID is best practice for mitigation of pain following cautery disbudding of calves.

EXPERT'S CONCLUDING COMMENTS

We are very fortunate that this is an area of veterinary medicine that has enough primary research available to conduct a systematic review and meta-analysis, the highest quality scientific evidence available. Accepting that some limitations remain, predominantly associated with deficiencies in the underlying studies, this is a high-quality review conducted by a high-quality research group.

As I concluded in a separate piece on this subject,[18] as a profession, we should be honest with ourselves and accept that the most significant barriers to the use of multimodal analgesia for disbudding are not based on the available scientific evidence. Instead, they are issues of industry culture, farm protocols, and established practice norms. Driving change requires leadership and an understanding and then acceptance of the necessity for change.

Further information on this type of approach and how it is driving evidence-based decision making in human health can be found on the Cochrane website (www.cochrane.org).

TAKE-HOME MESSAGES:

- Pain management for the disbudding of calves has become a prominent animal welfare issue in the beef and dairy industry.
- Systemic reviews provide a stronger level of evidence than a single research study or narrative review.
- Based on qualitative synthesis and meta-analyses of data from 17 research studies:
  - Local aesthetic was associated with reduced plasma cortisol level until 2hrs post-disbudding followed by a rise in cortisol observed at 4hrs post-disbudding.
  - Adding an NSAID to local anaesthetic resulted in a reduction in plasma cortisol level at 4hrs and reductions in pressure tolerance and pain behaviours at 3–6hrs post-disbudding.
- Based on these results, use of local anaesthetic and an NSAID is recommended as best practice for pain mitigation for cautery disbudding of calves aged ≤12 weeks.
- Wide variation among studies prevented the recommendation of specific NSAIDs.

REFERENCES

1. Stock ML, et al. Bovine dehorning: assessing pain and providing analgesic management. Vet Clin North Am Food Anim Pract. 2013;29(1):103-33.
2. Herskin MS, et al. Welfare Effects of the Use of a Combination of Local Anesthesia and NSAID for Disbudding Analgesia in Dairy Calves-Reviewed Across Different Welfare Concerns. Front Vet Sci. 2018;5:117.
3. Parliamentary Counsel Office. Animal Welfare (Care and Procedures) Regulations 2018 (LI 2018/50). Wellington: New Zealand Parliamentary Counsel Office. 2018. Last update date: 26/03/18. Available from: http://www.legislation.govt.nz/regulation/public/2018/0050/latest/whole.html#LMS22929. [Date accessed: 03/09/19].
4. New Zealand Veterinary Association. Policy: Disbudding and dehorning of cattle. Wellington: New Zealand Veterinary Association. Last update date: May 2019. Available from: https://www.nzva.org.nz/page/policydehorning. [Date accessed: 12/08/19].
5. Winder CB, et al. Effects of local anesthetic or systemic analgesia on pain associated with cautery disbudding in calves: A systematic review and meta-analysis. J Dairy Sci. 2018;101(6):5411-27.
6. Sargeant JM, et al. Introduction to systematic reviews in animal agriculture and veterinary medicine. Zoonoses Public Health. 2014;61 Suppl 1:3-9.
7. Higgins JP, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
8. Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. J Stat Softw. 2010;36(3):48.
9. Stafford KJ, et al. Dehorning and disbudding distress and its alleviation in calves. Vet J. 2005;169(3):337-49.
10. Coetzee JF, et al. Pharmacokinetics and effect of intravenous meloxicam in weaned Holstein calves following scoop dehorning without local anesthesia. BMC Vet Res. 2012;8:153.
11. Lohuis JA, et al. Pharmacodynamics and pharmacokinetics of carprofen, a non-steroidal anti-inflammatory drug, in healthy cows and cows with Escherichia coli endotoxin-induced mastitis. J Vet Pharmacol Ther. 1991;14(3):219-29.
12. Landoni MF, et al. Pharmacokinetics and pharmacodynamics of ketoprofen in calves applying PK/PD modelling. J Vet Pharmacol Ther. 1995;18(5):315-24.
13. Gingerich DA, et al. Pharmacokinetics and dosage of aspirin in cattle. J Am Vet Med Assoc. 1975;167(10):945-8.
14. Anderson KL, et al. Pharmacokinetics of flunixin meglumine in lactating cattle after single and multiple intramuscular and intravenous administrations. Am J Vet Res. 1990;51(9):1464-7.
15. Mintline EM, et al. Play behavior as an indicator of animal welfare: Disbudding in dairy calves. Appl Anim Behav Sci. 2013;144(1):22-30.
16. Sargeant JM, et al. Conducting systematic reviews of intervention questions II: Relevance screening, data extraction, assessing risk of bias, presenting the results and interpreting the findings. Zoonoses Public Health. 2014;61 Suppl 1:39-51.
17. Sargeant JM, et al. The REFLECT statement: reporting guidelines for randomized controlled trials in livestock and food safety: explanation and elaboration. J Food Prot. 2010;73(3):579-603.
18. Animal Health Reivew. Product Review: Meloxicam and disbudding in dairy calves. Auckland: Research Review. 2019. Available from: https://www.animalhealthreview.co.nz/getmedia/50dee536-acf7-409f-ae2d-31825732cad7/PR-Meloxicam.pdf.aspx?ext=.pdf

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