Assessment and Management of Pain Associated with Castration in Cattle

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KEYWORDS

• Castration • Cattle • Pain assessment • Analgesia • Animal welfare

KEY POINTS

- Validated pain assessment tools are needed to support approval of analgesic compounds to alleviate pain associated with castration.
- Accelerometers, videography, heart rate variability determination, electroencephalography, thermography, and plasma neuropeptide measurement have been used to assess behavioral, physiologic, and neuroendocrine changes associated with castration.
- Preemptive administration of a nonsteroidal antiinflammatory drug (NSAID) and local anesthesia significantly decreases peak serum cortisol concentration after castration.
- Local anesthesia alone tends to decrease peak cortisol concentrations more than NSAIDs, whereas NSAIDs alone tend to decrease the area under the cortisol-time curve more than local anesthesia alone.

INTRODUCTION

Castration of male calves destined for beef production is one of the most common livestock management practices performed in the United States amounting to approximately 7 million procedures per year.[1] Methods of castration are typically associated with physical, chemical, or hormonal damage to the testicles.[2] In most production settings, physical castration methods are the most common. These can be subdivided into procedures involving surgical removal of the testes, or methods that irreparably

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damage the testicles by interruption of the blood supply using a castration clamp (burdizzo castration), a rubber ring, or a latex band.[3]

The benefits of castration include a reduction in aggression and mounting behavior of males resulting in fewer injuries in confinement operations and reduced dark-cutting beef.[4] Steers also have higher meat quality with increased tenderness and marbling. Carcasses from steers therefore command higher prices at market compared with bulls.[3] Castration also prevents physically or genetically inferior males from reproducing and prevents pregnancy in commingled pubescent groups.[2] Although the benefits of castration are widely accepted in most countries, all castration methods have been demonstrated to produce physiologic, neuroendocrine, and behavioral changes indicating pain and distress.[2,5–10]

Societal concern about the moral and ethical treatment of animals is becoming more prevalent.[11] In particular, negative public perception of pain associated with castration procedures is mounting, with increasing calls for the development of practices to relieve pain and suffering in livestock.[12] Preemptive analgesia can be applied in advance of the painful stimulus thereby reducing sensitization of the nervous system to subsequent stimuli that could amplify pain. Agents that could be used to provide preemptive analgesia include local anesthetics, nonsteroidal antiinflammatory drugs (NSAIDs), opioids, α2-agonists, and *N*-methyl-D-aspartate receptor antagonists.[13] The American Veterinary Medical Association "supports the use of procedures that reduce or eliminate the pain of dehorning and castrating of cattle" and proposes that "available methods of minimizing pain and stress include application of local anesthesia and the administration of analgesics." Despite this, a recent survey of bovine veterinarians conducted by our research group found that only 1 in 5 survey respondents use anesthesia or analgesics at the time of castration.[14] Furthermore, 90% of respondents indicated that they castrate and dehorn cattle at the same time although there are few studies examining the effect of this on the animal in the literature.

It is remarkable that although administration of local anesthesia before castration and dehorning is legislated in several European countries,[15] there are currently no analgesic drugs specifically approved for pain relief in livestock by the US Food and Drug Administration (FDA).[16] FDA Guidance Document 123 for the development of effectiveness data for NSAIDs states that "validated methods of pain assessment must be used in order for a drug to be indicated for pain relief in the target species."[17] The identification and validation of robust, repeatable pain measurements is therefore fundamental for the development and approval of effective analgesic drug regimens for use in livestock.

The development of robust biomarkers for the objective measurement of pain is necessary for evaluating the efficacy of analgesic treatment regimens during routine animal husbandry procedures such as castration and dehorning. This process is especially complex in a prey species, such as cattle, that inherently conceal pain.[18] Pain is defined as "an aversive feeling or sensation associated with actual or potential tissue damage resulting in physiologic, neuroendocrine, and behavioral changes that indicate a stress response."[19] In previous research, markers for the evaluation of pain and distress associated with noxious animal husbandry procedures have focused on assessing behavioral, physiologic, and neuroendocrine changes. A change in animal behavior has been assessed using visual pen scoring,[20] videography,[9] vocalization,[9,21] measurement of chute exit speed,[22–24] pedometers,[9] and accelerometers.[25] Physiologic changes have been assessed using serum cortisol measurement,[2] heart rate determination,[26] feed intake, and average daily gain (ADG).[27,28] Neuroendocrine changes have been assessed through measurement of the neuropeptide substance

P[21], infrared thermography,[29,30] heart rate variability (HRV),[29–31] skin electrical impedance (electrodermal activity),[24,32] and electroencephalography (EEG).[33,34] Several of these tools have also been used to assess the efficacy of analgesic compounds.

This review discusses the options for providing analgesia to calves before castration and the tools that have been used to assess analgesic drug efficacy. Published evidence to support the effect of analgesic compounds on physiologic, neuroendocrine, and behavioral changes associated with castration is also reviewed. Publications were identified on PubMed using the search terms "Castration" and "Bovine" and "Analgesia." Studies that compared pain biomarkers in castrated control calves with calves treated with an analgesic before castration were used to determine a percent change associated with drug treatment (**Tables 1** and **2**).

ASSESSMENT TOOLS USED TO DETERMINE THE EFFICACY OF ANALGESIC DRUGS IN CATTLE AFTER CASTRATION

Assessment of Behavioral Changes After Castration

Assessment tools that have been used to quantify changes in animal behavior following castration include visual scoring systems,[26] videography,[9,10] vocalization,[9] chute behavior,[9] pedometers,[9] and accelerometers.[25]

The literature on behavioral responses associated with castration has been summarized in a review by Stafford and Mellor.[2] The investigators concluded that assessments of individual animal behavioral changes in response to pain are highly subjective. Escape behaviors demonstrated at castration but not seen afterward may reflect a pain response[35] or a desire to escape confinement.[36] Fell and colleagues[36] reported that surgically castrated calves struggle and kick during the procedure but calves castrated with rubber rings are quieter. Macauley and colleagues[37] found that calves castrated surgically were less active than control calves or calves castrated using a burdizzo. Robertson and colleagues[38] found that rubber ring, burdizzo, and surgical castration caused significant behavioral responses indicating pain during the first 3 hours after castration. Fisher and colleagues[39] found that 14-month-old bulls castrated surgically stamped their hind feet, swished their tails, and grazed less after castration than control bulls and bulls castrated using bands. Behaviors indicating a painful sensation such as turning the head toward the hindquarters, alternate lifting of the hind legs, abnormal postures, and slow movement of the tail have been reported weeks after rubber ring castration.[40]

Currah and colleagues[9] and González and colleagues[10] used videography to determine the stride length of calves before and after surgical and band castration, respectively. Both studies reported that stride length was significantly shortened after castration. Furthermore, Currah and colleagues[9] concluded that calves took significantly fewer steps after surgical castration in a study that used pedometers to compare step count before and after the procedure. In the same study, only 10 of 71 calves (14%) vocalized during castration and no difference in chute behavior assessed using load cells was reported. White and colleagues[25] used accelerometers to evaluate standing and laying behavior in calves before and after surgical castration. The study concluded that calves spent significantly more time standing after castration.

Assessment of Physiologic Changes After Castration

Physiologic changes after castration have been assessed using serum cortisol, heart rate, feed intake, and ADG measurements.

Table 1
Summary of the scientific literature examining the effect of analgesic drug administration on plasma cortisol response in castrated calves

References	Procedure	Study Population	Analgesic Regimen	Outcome Parameter	Percent Change in Cortisol (%)	Significance (*P* Value)
Faulkner et al,[63] 1992	Surgical Castration	6–9 mo beef	Xylazine 0.02 mg/kg and butorphanol 0.07 mg/kg IV 90 s before castration	Cortisol (day 3)	−10.03	NS
Fisher et al,[5] 1996	Burdizzo clamp castration	5.5 mo dairy	Lidocaine local anesthesia, 8 mL/testicle, 15 min before castration	Cortisol (Cmax)	−15.61	NS
				Cortisol AUEC	−13.15	NS
	Surgical castration		Lidocaine local anesthesia, 8 mL/testicle, 15 min before castration	Cortisol (Cmax)	−23.04	<0.05
				Cortisol AUEC	−21.97	<0.05
Earley and Crowe,[42] 2002	Surgical castration	5.5 mo dairy	Ketoprofen 3 mg/kg IV, 20 min before castration	Cortisol (Cmax)	−46.07	<0.05
				Cortisol AUEC	−55.65	<0.05
			Lidocaine local anesthesia, 6 mL/testicle, 20 min before castration	Cortisol (Cmax)	−51.75	<0.05
				Cortisol AUEC	−25.72	NS
			Ketoprofen 3 mg/kg IV and lidocaine local anesthesia, 6 mL/testicle administered 20 min before castration	Cortisol (Cmax)	−37.12	<0.05
				Cortisol AUEC	−33.22	<0.05
Stafford et al,[43] 2002	Rubber ring castration	2–4 mo dairy	Lidocaine local anesthesia, 3 mL/testicle, 20 min before castration	Cortisol (Cmax)	−68.42	<0.05
			Ketoprofen 3 mg/kg IV and lidocaine local anesthesia, 3 mL/testicle administered 20 min before castration	Cortisol (Cmax)	−55.26	<0.05
	Band castration		Lidocaine local anesthesia, 3 mL/testicle, 20 min before castration	Cortisol (Cmax)	−72.28	<0.05
			Ketoprofen 3 mg/kg IV and lidocaine local anesthesia, 3 mL/testicle administered 20 min before castration	Cortisol (Cmax)	−74.26	<0.05

Stafford et al,[43] 2002	Surgical castration (pull)	2–4 mo dairy	Lidocaine, 3 mL/testicle, 20 min before castration	Cortisol (Cmax)	−2.94	NS
			Ketoprofen 3 mg/kg IV and lidocaine local anesthesia, 3 mL/testicle administered 20 min before castration	Cortisol (Cmax)	−55.88	<0.05
	Surgical castration (cut)		Lidocaine, 3 mL/testicle, 20 min before castration	Cortisol (Cmax)	52.73	<0.05
			Ketoprofen 3 mg/kg IV and lidocaine local anesthesia, 3 mL/testicle administered 20 min before castration	Cortisol (Cmax)	−43.64	<0.05
	Burdizzo clamp castration		Lidocaine local anesthesia, 3 mL/testicle, 20 min before castration	Cortisol (Cmax)	−17.19	NS
			Ketoprofen 3 mg/kg IV and lidocaine local anesthesia, 3 mL/testicle administered 20 min before castration	Cortisol (Cmax)	−67.19	<0.05
Ting et al,[59] 2003	Burdizzo clamp castration	13 mo dairy	Ketoprofen 3 mg/kg IV, 20 min before castration	Cortisol (Cmax)	−33.76	<0.001
				Cortisol AUEC	−52.47	<0.001
			Lidocaine, 8 mL/testicle, 20 min before castration	Cortisol (Cmax)	−34.55	<0.001
				Cortisol AUEC	1.14	NS
			Xylazine 0.05 mg/kg and lidocaine 0.4 mg/kg Epidural, 10 min before castration	Cortisol (Cmax)	−24.65	<0.001
				Cortisol AUEC	14.07	NS
Ting et al,[60] 2003	Surgical castration	11 mo dairy	Ketoprofen 3 mg/kg IV, 20 min before castration	Cortisol (Cmax)	11.82	NS
				Cortisol AUEC	−41.67	<0.05
			Ketoprofen 1.5 mg/kg IV twice; 20 min before castration and repeated at castration	Cortisol (Cmax)	−2.95	NS
				Cortisol AUEC	−42.59	<0.05
			Ketoprofen 1.5 mg/kg IV, 20 min before castration, repeated at castration and 3 mg/kg at 24 h after castration	Cortisol (Cmax)	0.00	NS
				Cortisol AUEC	−26.54	<0.05

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Table 1
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References	Procedure	Study Population	Analgesic Regimen	Outcome Parameter	Percent Change in Cortisol (%)	Significance (*P* Value)
Pang et al,[6] 2006	Band castration	5.5 mo dairy	Carprofen 1.4 mg/kg IV, 20 min before castration	Cortisol (Cmax)	−18.74	NS
				Cortisol AUEC	−22.99	NS
	Burdizzo clamp castration		Carprofen 1.4 mg/kg IV, 20 min before castration	Cortisol (Cmax)	−4.07	NS
				Cortisol AUEC	−25.85	NS
Coetzee et al,[45] 2007	Surgical castration, Henderson castration tool	4–6 mo beef	Sodium salicylate 50 mg/kg IV <30 s before castration	Cortisol (Cmax)	−11.44	NS
				Cortisol AUEC	−6.33	NS
			Acetylsalicylic acid 100 mg/kg by mouth <30 s before castration	Cortisol (Cmax)	23.29	NS
				Cortisol AUEC	17.72	NS
Thüer,[66] 2007	Burdizzo clamp castration	<1 mo dairy	Lidocaine, 10 mL local anesthesia 5 min before castration	Cortisol (Cmax) estimated	−35.38	*P* = .014
	Band castration		Lidocaine, 10 mL local anesthesia 5 min before castration	Cortisol (Cmax) estimated	−25.00	NS
Stilwell,[8] 2008	Burdizzo clamp castration	6 mo old dairy	Lidocaine, 4 mL	Cortisol (6 h)	−41.38	NS
			Epidural administered 5 min before castration	Cortisol (24 h)	−22.41	NS
				Cortisol (48 h)	45.76	NS
			Flunixin meglumine 2.2 mg/kg SC and lidocaine, 4 mL	Cortisol (6 h)	−51.90	<0.05
				Cortisol (24 h)	−30.69	NS
			Epidural administered 5 min before castration	Cortisol (48 h)	30.37	NS
			Carprofen 1.4 mg/kg SC and lidocaine, 4 mL	Cortisol (6 h)	−58.89	<0.05
			Epidural administered 5 min before castration	Cortisol (24 h)	−47.52	<0.05
				Cortisol (48 h)	−36.48	<0.05
Boesch et al,[56] 2008	Burdizzo clamp castration	1 wk dairy	Lidocaine, 10 mL local anesthesia 20 min before castration	Cortisol (Cmax) estimated	−35.00	*P* = .061
			Bupivacaine, 10 mL local anesthesia 20 min before castration	Cortisol (Cmax) estimated	−29.17	NS

Gonzalez et al,[10] 2010	Band castration	210 d beef	Xylazine 0.07 mg/kg epidural and IV flunixin meglumine at 1.1 mg/kg	Salivary cortisol (4 h)	−59.84	0.03
				Salivary cortisol (24 h)	−26.04	0.31
				Salivary cortisol (14 d)	0.00	0.77
Coetzee et al,[14,65] 2010	Surgical castration, Henderson castration tool	4–6 mo beef	Xylazine 0.05 mg/kg IV <30 s before castration	Cortisol (Cmax)	−8.21	NS
				Cortisol AUEC	28.70	NS
			0.05 mg/kg xylazine and 0.1 mg/kg ketamine IV <30 s before castration	Cortisol (Cmax)	−8.69	NS
				Cortisol AUEC	22.50	NS
Stewart et al,[30] 2010	Surgical castration	4 mo dairy	Lidocaine, 5 mL into the scrotum followed by 7 mL at the neck of the scrotum	Cortisol (Cmax)	−39.67	P<.05
Webster et al,[61] 2010	Surgical castration, Henderson castration tool	2–3 mo dairy	Flunixin meglumine, 1.1 mg/kg IV, 20 min before castration	Cortisol (Cmax)	−26.37	NS
				Cortisol AUEC	−33.55	NS
			2% Lidocaine ring block (20 mL) and intratesticular (5 mL/testes), 20 min before castration	Cortisol (Cmax)	−10.56	NS
				Cortisol AUEC	−21.94	NS
			2% Lidocaine ring block (20 mL) and intratesticular (5 mL/testes) and flunixin meglumine 1.1 mg/kg IV, 20 min before castration	Cortisol (Cmax)	−48.16	NS
				Cortisol AUEC	−48.26	NS
Baldridge et al,[24] 2010	Surgical castration followed by surgical dehorning (Barnes)	2–4 mo dairy	Sodium salicylate at 2.5–5 mg/mL in the drinking water (13.62–151.99 mg of salicylate/kg bodyweight)	Cortisol (Cmax)	1.60	NS
				Cortisol AUEC (0–1 h)	−9.27	NS
				Cortisol AUEC (1–6 h)	−36.90	P<.05
				Cortisol AUEC (6–24 h)	−22.83	NS

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Table 1 (*continued*)

References	Procedure	Study Population	Analgesic Regimen	Outcome Parameter	Percent Change in Cortisol (%)	Significance (*P* Value)
			0.025 mg/kg butorphanol, 0.05 mg/kg xylazine, 0.1 mg/kg ketamine coadministered IM immediately before castration	Cortisol (Cmax)	−12.00	NS
				Cortisol AUEC (0–1 h)	−28.90	$P<.05$
				Cortisol AUEC (1–6 h)	−5.82	NS
				Cortisol AUEC (6–24 h)	−0.01	NS
			Sodium salicylate at 2.5–5 mg/mL in the drinking water (13.62–151.99 mg of salicylate/kg bodyweight) and 0.025 mg/kg butorphanol, 0.05 mg/kg xylazine, 0.1 mg/kg ketamine coadministered IM immediately before castration	Cortisol (Cmax)	−3.46	NS
				Cortisol AUEC (0–1 h)	−20.89	NS
				Cortisol AUEC (1–6 h)	−24.19	NS
				Cortisol AUEC (6–24 h)	−15.69	NS

Percent change in cortisol was calculated using the formula [(Mean of analgesic group/Mean of castrated control group) − 1] × 100.

Abbreviations: AUEC, area under the effect curve for cortisol; Cmax, maximum plasma concentration; IM, intramuscularly; IV, intravenously; SC, subcutaneously.

Table 2
Summary of scientific literature examining the effect of analgesic drug administration on other outcomes in castrated calves

References	Procedure	Study Population	Analgesic Regimen	Outcome Parameter	Percent Change (%)	Significance (*P* Value)
Faulkner et al,[63] 1992	Surgical castration	6–9 mo beef	Xylazine 0.02 mg/kg and butorphanol 0.07 mg/kg IV 90 s before castration	ADG (day 0–27)	−11.11	NS
				Feed intake (day 0–27)	−5.00	NS
				Gain/feed	−11.11	NS
				Morbidity (day 0–27)	−4.17	NS
				Mortality (day 0–27)	0.00	NS
Fisher et al,[5] 1996	Burdizzo clamp castration	5.5 mo dairy	Lidocaine local anesthesia, 8 mL/testicle, 15 min before castration	Feed intake (day 1–20)	0.49	NS
				ADG (day 0–35)	−1.15	NS
	Surgical castration		Lidocaine local anesthesia, 8 mL/testicle, 15 min before castration	Feed intake (kg) (day 1–20)	0.96	NS
				ADG (day 0–35)	32.79	*P*<.05
Earley and Crowe,[42] 2002	Surgical castration	5.5 mo dairy	Ketoprofen 3 mg/kg IV, 20 min before castration	Fibrinogen (day 35)	−8.43	*P*<.05
				Haptoglobin (day 35)	50.00	NS
				Feed intake (day 1–35)	−4.64	NS
				ADG (day 0–35)	71.43	NS
			Lidocaine local anesthesia, 6 mL/testicle, 20 min before castration	Fibrinogen (day 35)	−13.79	*P*<.05
				Haptoglobin (day 35)	50.00	NS
				Feed intake (day 1–35)	−2.79	NS
				ADG (day 0–35)	17.86	NS
			Ketoprofen 3 mg/kg IV and lidocaine local anesthesia, 6 mL/testicle administered 20 min before castration	Fibrinogen (day 35)	−28.93	*P*<.05
				Haptoglobin (day 35)	0.00	NS
				Feed intake (day 1–35)	−2.48	NS
				ADG (day 0–35)	96.43	*P*<.05
Ting et al,[59] 2003	Burdizzo clamp castration	13 mo dairy	Ketoprofen 3 mg/kg IV, 20 min before castration	Feed intake (day −1 to 33)	4.66	NS
				ADG (day −1 to 35)	46.51	NS
			Lidocaine, 8 mL/testicle, 20 min before castration	Feed intake (day −1 to 33)	−0.26	NS
				ADG (day −1 to 35)	0.00	NS
			Xylazine 0.05 mg/kg and lidocaine 0.4 mg/kg Epidural, 10 min before castration	Feed intake (day −1 to 33)	−0.26	NS
				ADG (day −1 to 35)	20.93	NS

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Table 2
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References	Procedure	Study Population	Analgesic Regimen	Outcome Parameter	Percent Change (%)	Significance (*P* Value)
Ting et al,[60] 2003	Surgical castration	11 mo dairy	Ketoprofen 3 mg/kg IV, 20 min before castration	Feed intake (day −1 to 33)	−0.82	NS
				ADG (day −1 to 35)	7.69	NS
			Ketoprofen 1.5 mg/kg IV twice; 20 min before castration and repeated at castration	Feed intake (day −1 to 33)	6.28	NS
				ADG (day −1 to 35)	−9.23	NS
			Ketoprofen 1.5 mg/kg IV, 20 min before castration, repeated at castration and 3 mg/kg at 24 h after castration	Feed intake (day −1 to 33)	2.73	NS
				ADG (day −1 to 35)	−18.46	NS
Pang et al,[6] 2006	Band castration	5.5 mo dairy	Carprofen 1.4 mg/kg IV, 20 min before castration	Fibrinogen (day 35)	−19.25	NS
				Haptoglobin (day 35)	−76.19	$P<.05$
				Rectal temperature	0.00	NS
	Burdizzo clamp castration		Carprofen 1.4 mg/kg IV, 20 min before castration	Fibrinogen (day 35)	−2.13	NS
				Haptoglobin (day 35)	0.00	NS
				Rectal temperature	0.26	NS
Gonzalez et al,[10] 2010	Band castration	210 d beef	Xylazine 0.07 mg/kg epidural and IV flunixin meglumine at 1.1 mg/kg	ADG (day 0–42)	0.00	0.21
				Feed intake (day 0–42)	−1.54	0.02
				Fecal *Escherichia coli*, log (cfu)	−10.16	0.9
				Lying time, %	29.65	0.1
				Step length (back)	−3.83	0.04
				Step length (front)	−1.03	0.38
Stewart et al,[30] 2010	Surgical castration	4 mo dairy	Lidocaine, 5 mL into the scrotum followed by 7 mL at the neck of the scrotum	Heart rate (0–2 min)	−58.82	<0.05
				Eye temperature (5–20 min after castration)	−40.43	<0.05
				HRV: LF power	−7.34	NS
				HRV: HF power	−7.34	NS
				HRV: LF/HF ratio	−76.19	NS

Baldridge et al,[24] 2010	Surgical castration followed by surgical dehorning (Barnes)	2–4 mo dairy	Sodium salicylate at 2.5–5 mg/mL in the drinking water (13.62–151.99 mg of salicylate/kg bodyweight)	ADG (day 0–13) Chute exit speed	1111.22 −0.97	<0.05 NS
			0.025 mg/kg butorphanol, 0.05 mg/kg xylazine, 0.1 mg/kg ketamine coadministered IM immediately before castration	ADG (day 0–13) Chute exit speed	729.98 77.81	NS <0.05
			Sodium salicylate at 2.5–5 mg/mL in the drinking water (13.62–151.99 mg of salicylate/kg bodyweight) and 0.025 mg/kg butorphanol, 0.05 mg/kg xylazine, 0.1 mg/kg ketamine coadministered IM immediately before castration	ADG (day 0–13) Chute exit speed	1095.92 94.97	<0.05 <0.05
Coetzee et al,[62] 2011	Surgical castration	8–10 mo (193–285 kg) beef	Meloxicam tablets at 1 mg/kg suspended in 50 mL of water in a dosing syringe and administered orally, 24 h before castration	ADG (day 1–14) DMI (day 1–14) G/F ratio (day 1–14) ADG (day 15–28) DMI (day 15–28) G/F ratio (15–28 d) Pull rate (%) Bovine respiratory disease treatment rate (%)	21.79 2.13 18.75 −2.6 0.86 −4.55 −42.92 −49.11	NS NS NS NS NS NS <0.05 <0.05

Percent change in cortisol was calculated using the formula [(Mean of analgesic group/Mean of castrated control group) − 1] × 100.

Abbreviations: ADG, average daily gain in body weight; cfu, colony forming units; DMI, Dry Matter Intake; G/F, Gain to Feed Ratio; HF, high frequency; HRV, heart rate variability; LF, low frequency.

Several studies have evaluated acute cortisol response as a method of determining the extent and duration of distress associated with castration in cattle.[19,40–43] Studies reviewed by Stafford and Mellor[2] indicate that surgical and latex band castrations, especially when performed in older cattle, seem to elicit higher plasma cortisol responses that remain higher than pretreatment levels for longer. The peak cortisol concentration after surgical castration occurs within the first 30 minutes after castration and ranges from 45 nmol/L after rubber ring castration to 129 nmol/L after surgical castration. The duration of plasma cortisol response higher than pretreatment levels typically ranges from 60 minutes after burdizzo castration to 180 minutes after surgical castration.

Cortisol has been widely used as a measurement of distress because its response magnitude, as indicated by peak height, response duration, and/or integrated response usually accords with the predicted noxiousness of different procedures.[35,44] At each end of the cortisol response range, however, interpretation is less straightforward. At the lower end, for example, studies have shown that tail docking with a ring and tail docking with a docking iron cause similar cortisol responses to control handling in older lambs.[19] At the upper end of the range, there are several examples in which cortisol responses do not increase proportionally to the severity of different treatments as might be expected. There may be a ceiling effect on plasma cortisol responses.[19,45] Other studies have shown that plasma cortisol concentration after surgical castrations varies greatly between animals.[43] Based on these data, it has been hypothesized that low responses may be due to individuals having a high pain threshold.[2] Variations may also come about because of differences in the way in which a particular castration method is performed by different operators. These data suggest that plasma cortisol levels may not always accurately reflect the extent of the pain response in animals.

Schwartzkopf-Genswein and colleagues[26] evaluated the heart rate in 15 calves before and after surgical castration. Heart rates were significantly lower at 15 and 30 minutes after castration compared with precastration rates. However, there was a significant increase in heart rate at 120 minutes after castration. The investigators concluded that castration had little effect on heart rate. However, these results may have been confounded because calves had been dehorned 21 days previously and the overall heart rates were higher before and after castration than they were in the period before the dehorning.

Production parameters are often too imprecise to reflect the pain experienced by animals after castration.[2] Furthermore, weight gain after castration may be negatively influenced by a decrease in testosterone after removal of the testes.[46] However, assessment of production parameters is critical if research on animal well-being is to have relevance to livestock producers. In studies reviewed by Stafford and Mellor,[2,46,47] burdizzo or surgical castration was found to have no effect on ADG over a 3-month period after castration. However, the ADG of 7-week-old calves during the 5 weeks after castration using rubber rings, a clamp, or surgery was found to be lower than noncastrated calves but similar between the different castration methods.[46] Rubber ring and surgical castration were reported to cause a decrease in ADG of 50% and 70%, respectively, in cattle aged 8 to 9 months.[48] When 8-, 9-, and 14-month-old cattle were castrated surgically or using latex bands, cattle castrated later had poorer growth rates than those castrated at weaning. Cattle castrated with latex bands also had lower growth rates than those castrated surgically during the following 4 to 8 weeks.[39,47]

In a study conducted by Oklahoma State University, 162 bull calves were used to determine the effects of latex banding of the scrotum or surgical castration on growth rate. Bulls that were banded at weaning gained less weight than bulls that were banded or surgically castrated at 2 to 3 months of age.[27] In a second study, 368 bull calves were used in 2 separate experiments to examine the effect of the method of castration on health and performance. In the first experiment, latex banding of intact males shortly after arrival was found to decrease daily gain by 19% compared with purchasing steers, and by 14.9% compared with surgically castrating intact males shortly after arrival. In the second experiment, purchased castrated males gained 0.26 kg (0.58 lb) more and consumed 0.57 kg (1.26 lb) more feed per day than intact males surgically castrated shortly after arrival.[28]

Assessment of Neuroendocrine Changes After Castration

Neuroendocrine changes have been assessed through measurement of the neuropeptide substance P,[21] infrared thermography,[29,30] HRV,[29–31] electrodermal activity,[24,32] and EEG.[33,34]

Substance P is an 11-amino acid prototypic neuropeptide that regulates the excitability of dorsal horn nociceptive neurons and is present in areas of the neuroaxis involved in the integration of pain, stress, and anxiety. One study found that plasma substance P concentrations are up to 27-fold greater in human patients with soft tissue injury than healthy controls.[49] In a recent study to evaluate plasma substance P and cortisol response after castration, no significant difference in plasma cortisol response between castrated and uncastrated calves was observed over time (P = .644).[21] In contrast, mean plasma substance P concentrations were significantly higher in castrated calves compared with uncastrated controls over the course of the study (P = .042). Significant increases in plasma substance P concentration after castration suggest that this measurement may be associated with nociception although further investigation is necessary.

Infrared thermography evaluates changes in surface temperature.[29] Epinephrine release associated with castration causes changes in sympathetic tone. The adrenergic effects on cutaneous blood flow cause changes in skin temperature that can be quantified with a thermography camera (**Fig. 1**). A decrease in eye temperature observed after castration of calves without local anesthetic has been attributed to sympathetically mediated alterations in blood flow in capillary beds.[30]

HRV measurement assesses the variation in the intervals separating consecutive heart beats.[31] HRV is used to investigate the functioning of the autonomic nervous system, especially the balance between sympathetic and vagal activity.[31] It has been hypothesized that HRV measurement provides a more detailed measure of a stress response than heart rate alone.[29] This is because HRV makes it possible to measure the balance between sympathetic and parasympathetic tone, therefore

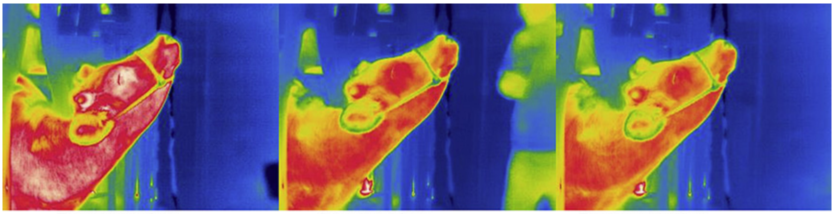

Fig. 1. Time sequence thermography images taken before castration, at the time of castration, and immediately after castration in a Holstein calf. Color changes likely indicate changes in peripheral perfusion associated with catecholamine release following castration.

providing a more detailed interpretation of autonomic activity.[31] HRV data are analyzed using frequency domain measures including high-frequency (HF) power (0.30–0.80 Hz), low-frequency (LF) power (0.04–0.30 Hz), and the LF/HF ratio. These outcomes are calculated by fast Fourier transformation.[29,30]

Recently, Stewart and colleagues[30] observed a significant increase in HF power from baseline in calves castrated surgically without local anesthesia. In contrast, a significant decrease in LF power compared with baseline was observed in calves castrated surgically with local anesthesia. The investigators concluded that an increase in HF power indicates an increase in parasympathetic activity that may be associated with deep visceral pain, as might occur when the spermatic cords are torn.

Electrodermal activity (EDA) is the electrical resistance between 2 electrodes applied to the skin.[50] EDA can be influenced by changes in resistance as a result of changes in sympathetic outflow. The Pain Gauge (Public Health Information Systems, Inc, Dublin, OH) is purported to be capable of measuring EDA although there is a paucity of data to support this use in livestock species. A study that used the Pain Gauge in rats found it ineffective for accurately assessing postoperative pain because pain scores did not decrease with increasing dosages of analgesic regimens.[51] Similar results were reported by Kotschwar and colleagues[32] in calves subjected to an amphotericin B lameness model. Baldridge and colleagues[24] observed a significant decrease in EDA measurement coinciding with the presence of quantifiable plasma xylazine, ketamine, and butorphanol concentrations. After 90 minutes, EDA increased and was not significantly different from other treatment groups. A difference in EDA between a sham and actual castration and dehorning period both with analgesia was not observed. Therefore, it was concluded that EDA measurement was not a reliable indicator of pain associated with dehorning and castration in calves and that EDA effects were likely associated with other physiologic changes associated with drug exposure.

EEG responses of calves to noxious stimuli associated with scoop dehorning using a minimal anesthesia model have been studied.[33] However, the use of general anesthesia may have confounded these results. Further studies are needed to determine the relevance of this research to understanding pain in conscious calves. Our research group is currently investigating the effect of age and method of castration on EEG response in conscious calves.[34] **Fig. 2** represents the EEG taken from a fully conscious, 12-week-old Holstein calf before and after surgical castration. Before castration, a distinct, low-frequency wave pattern predominates. Immediately after castration, there is a significant shift toward high-frequency, low-amplitude brain activity (beta frequency). The relative power of the low-frequency and high-frequency waves decreased and increased between baseline and castration periods, respectively. This activity is known as desynchronization of waves and is associated with nociception.[33] Delta bands showed a tendency toward an increase during the first recovery period suggesting attempted synchronization within 5 to 10 minutes after castration. The results of this study suggest that EEG may be a sensitive and specific measure of changes in brain electrical activity associated with castration.

ANALGESIC STRATEGIES AND THEIR EFFECTS ON PAIN BIOMARKERS

Local Anesthesia

One technique for providing local anesthesia of the testicles before castration has been previously described by Skarda.[52] Proper restraint and scrotal disinfection are recommended before commencing this procedure. In this approach, the testicle is grasped individually within the scrotum so that the overlying skin is tensed, which

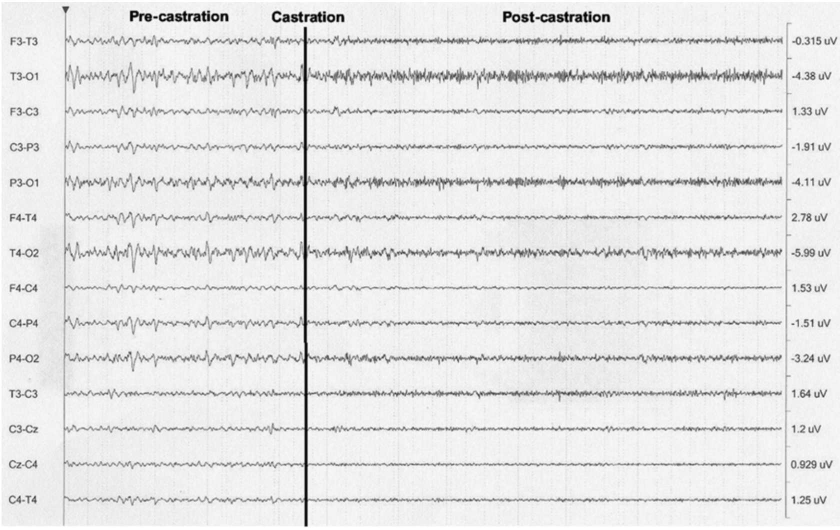

Fig. 2. Example of an EEG trace (30 s duration) illustrating brain electrical activity in a 6-week-old calf at castration. Note the transition in wave activity between the precastration period (calf restrained into the chute), castration (beginning of the procedure), and the postcastration period. There is a shift from a medium high-amplitude slow-frequency wave activity to low-amplitude fast-frequency EEG wave pattern (bipolar montage; time constant = 0.3 s; high-frequency filter = 70 Hz; notch filter inserted, amplitude-integrated EEG 2–30). (*Courtesy of* Dr Luciana Bergamasco, Kansas State University.)

facilitates the infiltration of 3 to 5 mL of 2% lidocaine subcutaneously along the line of incision. In bulls that weigh more than 200 kg, a 16 to 18 gauge needle measuring 3.75 to 7.5 cm is inserted below the tail of the epididymis toward the center of the testicle at an angle approximately 30° from perpendicular and 10 to 15 mL of 2% lidocaine are injected into each testicle (**Fig. 3**). In calves less than 200 kg, a 20 gauge needle measuring 2.5–3.75 cm is used to inject 2 to 10 mL of local anesthetic into the center of the testicle.

A second approach described by Rust and others involves the administration of 10 mL of 2% lidocaine subcutaneously along the circumference of the neck of the scrotum (**Fig. 4**A, B) followed by placement of 5 mL of a 2% lidocaine solution into each spermatic cord (see **Fig. 4**C, D).[53] After administration of lidocaine blocks, the bulls are released and run back through the chute for the treatment procedure after a 10-min waiting period to allow for the local anesthesia to take effect.

An overdose of local anesthesia can occur after accidental intravenous injection resulting in cardiac sodium channels becoming blocked so that conduction and automaticity become adversely depressed.[54] Generally, bupivacaine is considered more cardiotoxic than lidocaine. Aspiration before administration of local anesthetics is recommended to avoid accidental intravascular administration. The toxic dose of lidocaine and bupivacaine in cattle is considered to be 10 mg/kg and 3 to 4 mg/kg, respectively. Signs of overdose include sedation, twitching, convulsions, coma, and death.

Effect of Local Anesthesia on Biomarkers of Pain and Distress in Cattle at Castration

Lidocaine and bupivacaine have been examined as potential local anesthetics for use before bovine castration (see **Table 1**). Lidocaine has a fairly rapid onset of activity

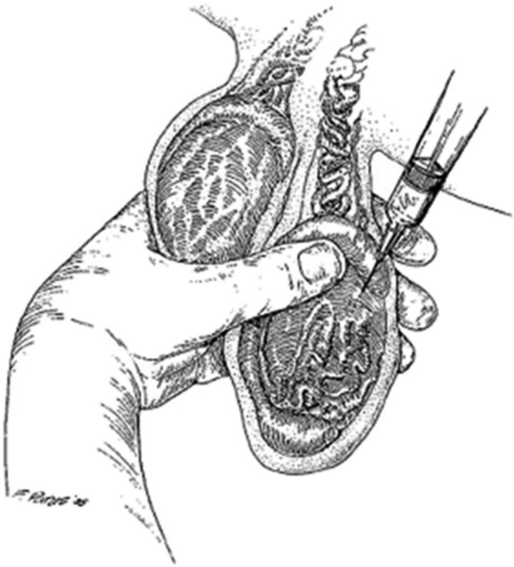

Fig. 3. Placement of an intratesticular local anesthetic injection for testicular block before castration. (*From* Skarda RT. Techniques of local analgesia in ruminants and swine. Vet Clin North Am Food Anim Pract 1986;2:621–63; with permission.)

(2–5 minutes), an intermediate duration of action (90 minutes), and a lower toxicity than bupivacaine.[55] Bupivacaine is the most potent long-acting amide local anesthetic with a slower onset of activity (20–30 minutes) but a longer duration of action (5–8 hours).[55] Boesch and colleagues[56] reported a similar reduction in plasma cortisol concentrations

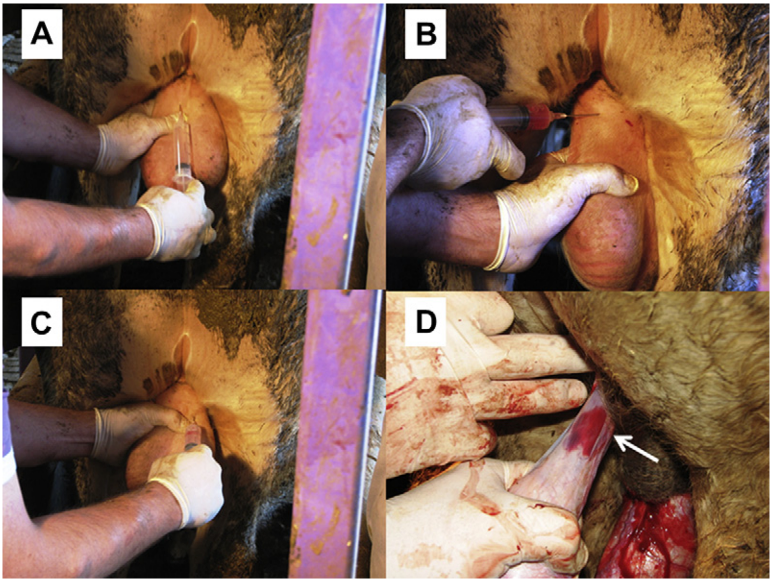

Fig. 4. Administration of 10 mL of 2% lidocaine subcutaneously along the circumference of the neck of the scrotum (*A*, *B*) followed by placement of 5 mL of a 2% lidocaine solution into each spermatic cord (*C, D*). (*Courtesy of* Dr Dan Thompson, Kansas State University.)

in 1-week-old dairy calves treated with lidocaine and bupivacaine before burdizzo clamp castration. This result suggests that bupivacaine may not offer significant clinical advantages over lidocaine possibly because of the slower onset of activity.

Surveys report that 10% of New Zealand producers,[57] 43% of British veterinarians,[58] and 22% of US veterinarians[14] administer local anesthetics before castration. A review of the literature identified 8 studies evaluating the effect of local anesthesia on plasma cortisol concentration after surgical and nonsurgical castration (see **Table 1**). The average percent reduction in peak plasma cortisol concentration (Cmax) in calves receiving local anesthesia alone before castration compared with castrated controls was 25.8% (95% confidence interval [CI] 2.46%–49.1%). However, the average area under the effect curve (AUEC) for cortisol was only reduced by 16.3% (95% CI 2.91%–29.7%) (**Fig. 5**). This result suggests that local anesthetics alone are effective in reducing acute distress associated with castration. However, the overall AUEC is only modestly reduced in calves receiving local anesthesia before castration likely due to the absence of analgesic and antiinflammatory effects extending into the postoperative period.

Several studies have evaluated the effect of local anesthetic administration before castration on feed intake, average daily weight gain, and inflammatory mediators (see **Table 2**). In most cases, the results of these studies have not shown a significant difference in performance between treated and control calves.[5,59,60] Recently, Stewart and colleagues[30] observed significant differences in heart rate and eye temperature in calves castrated with local anesthesia compared with untreated castrated controls. Changes were also observed in HRV, however the extent of this change from baseline levels in the castrated groups was not statistically significant.

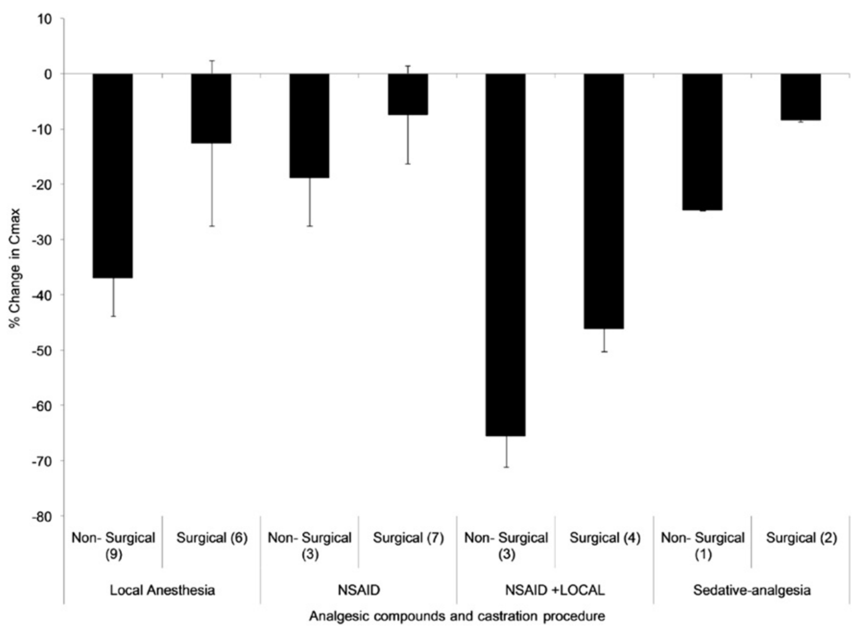

Fig. 5. Summary of the mean (±SEM) percent change in peak plasma cortisol concentrations (Cmax) in calves treated with analgesic compared with untreated castrated control calves in the published literature. The number of treatment groups evaluated is indicated in parentheses. Percent change in cortisol was calculated using the formula [(Mean of analgesic group/Mean of castrated control group) − 1] × 100.

NONSTEROIDAL ANTIINFLAMMATORY DRUGS (NSAIDs)

A review of the literature identified 8 studies evaluating the effect of NSAIDs alone on plasma cortisol concentration after surgical and nonsurgical castration (see **Fig. 5**). The average percent reduction in peak plasma cortisol concentration (Cmax) in calves receiving only an NSAID before castration compared with castrated control calves was 10.8% (95% CI 4.2% increase to 25.9% decrease in cortisol). However, the AUEC for cortisol was reduced by an average of 29% (95% CI 13.2%–44.8% reduction) (**Fig. 6**). This result suggests that NSAIDs alone are not effective in reducing acute distress associated with castration. However, the reduction in overall AUEC was greater in calves receiving an NSAID compared with calves administered only local anesthesia before castration. This result is likely due to the analgesic and antiinflammatory effects of NSAIDs extending into the postoperative period.

Most studies examining the effect of NSAIDs on pain biomarkers after bovine castration have involved administration of the analgesic 20 minutes before the start of the procedure. This procedure was presumably used to ensure adequate analgesic drug concentrations in the tissues at the time of castration. However, this significantly diminishes the external validity of these studies because such a delay is impractical in field situations. Future studies should examine the effect of drug administration at the time of the procedure so that the results are relevant to typical livestock production settings.

Earley and Crowe[42] and Stafford and colleagues[43] demonstrated a significant reduction in peak plasma cortisol concentrations in calves that were administered a combination of local anesthesia and an NSAID before castration compared with calves receiving either drug alone (see **Table 1**). The average percent reduction in peak plasma cortisol

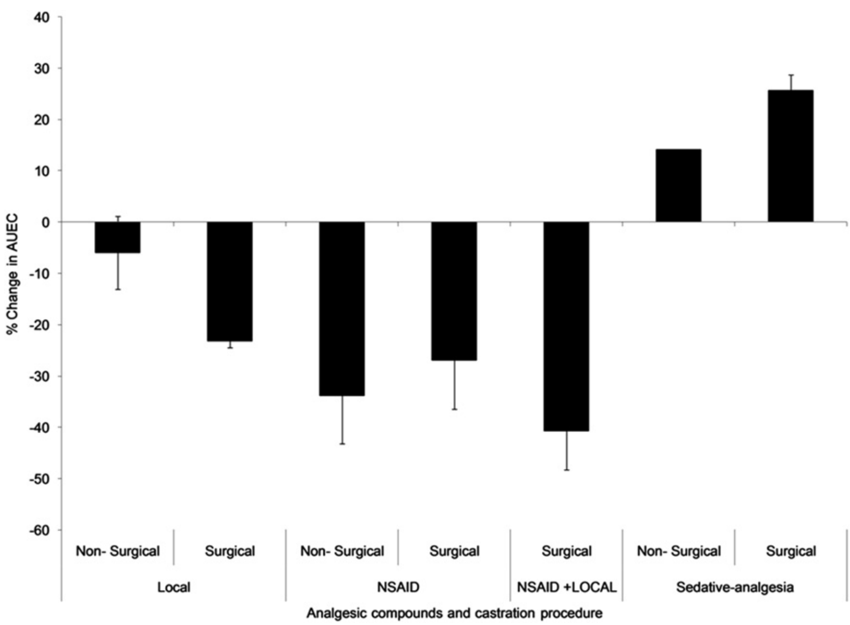

Fig. 6. Summary of the mean (±SEM) percent change in area under the plasma cortisol concentration over time curve (AUEC) in calves treated with analgesic compared with untreated castrated control calves in the published literature. The number of treatment groups evaluated is indicated in parentheses. Percent change in cortisol was calculated using the formula [(Mean of analgesic group/Mean of castrated control group) − 1] × 100.

concentration (Cmax) in calves receiving local anesthesia and an NSAID before castration compared with castrated control calves was 54.5% (95% CI 42.5%–66.53% decrease in cortisol) compared with 25.8% (95% CI 2.46%–49.1%) for local anesthesia alone and 10.8% (95% CI 4.2% increase to 25.9% decrease in cortisol) for NSAID alone (see **Fig. 5**). These results indicate that a multimodal analgesic approach using drugs that act on different receptors in the nociceptive pathway is more effective in mitigating pain associated with castration than a single analgesic agent.

Flunixin Meglumine

Stillwell and colleagues[8] reported that flunixin meglumine (2.2 mg/kg) combined with lidocaine epidural administration 5 minutes before burdizzo clamp castration decreased plasma cortisol concentration at 6 hours after castration by 50% compared with castrated control calves (see **Table 1**). However, at 48 hours after castration, the plasma cortisol concentration was 30% higher in flunixin-treated calves compared with control calves although this difference was not statistically significant. Currah and colleagues[9] observed that beef calves receiving 2.2 mg/kg flunixin meglumine combined with a lidocaine epidural took significantly more steps after surgical castration than castrated control calves. Furthermore, stride length was significantly greater in calves receiving flunixin than untreated calves at 4 and 8 hours after castration; however, at 12 hours there was no difference in the treatment groups.

González and colleagues[10] reported that salivary cortisol concentrations were 60% lower at 4 hours after band castration in calves receiving xylazine epidural and flunixin meglumine (1.1 mg/kg) compared with castrated controls. However, this difference was less evident at 24 hours and 14 days after castration. Stride length and feed intake were also significantly less in flunixin-treated calves compared with castrated controls. Webster and colleagues[61] found that peak plasma cortisol concentrations were 26% lower in calves receiving 2.2 mg/kg flunixin intravenously (IV) at 20 minutes before surgical castration compared with untreated calves. Calves that were administered a combination of lidocaine local anesthesia and flunixin meglumine IV had 48% lower peak plasma cortisol concentrations compared with castrated control calves. Neither of these differences was statistically significant.

Ketoprofen

Single or multiple doses of ketoprofen administered alone or in combination with local anesthesia before castration in cattle have been studied (see **Tables 1** and **2**).[42,59,60] Administration of ketoprofen without local anesthesia before castration reduced plasma cortisol concentrations by an average of 14% (95% CI 16.2% increase to 44.63% decrease in cortisol). However, the combination of local anesthesia and ketoprofen markedly reduced plasma cortisol concentrations by an average of 56% (95% CI 41% to 70% decrease) compared with castrated controls. These studies suggest that ketoprofen is more effective if combined with local anesthesia as part of a multimodal analgesic protocol.

Salicylic Acid Derivatives

A study was conducted to examine the effect of oral aspirin and intravenous sodium salicylate on plasma cortisol response after surgical castration in bulls.[45] Twenty bulls were randomly assigned to 1 of 4 groups (n = 5 bulls per treatment): (1) uncastrated, untreated control group; (2) castrated, untreated group; (3) castrated group receiving 50 mg/kg sodium salicylate IV immediately before castration; and (4) castrated group receiving 50 mg/kg aspirin (acetylsalicylic acid) orally immediately before castration. After castration or simulated castration, blood samples for salicylate and cortisol determination were collected at 3, 10, 20, 30, 40, 50 minutes and 1, 1.5, 2, 4, 6, 8, 10, and 12 hours after castration using a preplaced jugular catheter.

Oral aspirin administered at 50 mg/kg did not achieve quantifiable plasma salicylate concentrations in cattle. Mean plasma cortisol concentrations in this group were also the highest. In contrast, IV sodium salicylate significantly mitigated the mean plasma cortisol response at 30, 50, and 120 minutes after administration ($P<.05$). This effect was negated when plasma salicylate concentrations decreased to less than 20 μg/mL. Plasma sodium salicylate concentration decreased to less than the limit of quantitation by 240 minutes after IV injection. These results demonstrate that oral aspirin administered at 50 mg/kg does not achieve therapeutic concentrations in cattle. Furthermore, a sodium salicylate–mediated decrease in plasma cortisol response occurred in animals treated with IV sodium salicylate immediately before castration. This effect became less evident once plasma salicylate concentrations decreased to less than 20 μg/mL suggesting that this may be the minimum pain inhibitory concentration for salicylate in plasma.

Salicylate is more soluble than aspirin and may offer a convenient and cost-effective means of providing free-choice access to an NSAID in drinking water. Baldridge and colleagues[24] found that calves receiving 2.5 to 5 mg of sodium salicylate/mL of water beginning 72 hours before concurrent surgical castration and dehorning and continuing for 48 hours after surgery had a higher average daily weight gain for 13 days after castration/dehorning than untreated calves. However, water consumption decreased over the course of treatment suggesting that the inclusion of sodium salicylate had a negative effect on water palatability. Calves receiving sodium salicylate also has a significantly lower AUEC for cortisol in the period 1 to 6 hours after castration/dehorning.

Carprofen

Pang and colleagues[6] observed that carprofen administered at 1.4 mg/kg IV, 20 minutes before band castration reduced peak plasma cortisol concentrations by 19% compared with castrated control calves (see **Table 1**). However, this difference was not statistically significant. Carprofen-treated calves demonstrated a significant reduction in plasma haptoglobin concentrations (see **Table 2**). These effects were less in calves castrated with a burdizzo clamp. Stilwell and colleagues[8] reported a 59% reduction in plasma cortisol concentrations at 6 hours and a 36% reduction at 48 hours after burdizzo clamp castration in calves receiving 1.4 mg/kg carprofen combined with a lidocaine epidural compared with castrated controls.

Meloxicam

In a recent study, our group reported that meloxicam administration before castration in post weaning calves reduced the incidence of respiratory disease at the feedlot.[62] These findings have implications for developing NSAID protocols for use in calves at castration with respect to addressing animal health and welfare concerns.

SEDATIVE-ANALGESIC DRUGS

Opioid Analgesics

Faulkner and colleagues[63] investigated the health and performance effects of intravenous butorphanol (0.07 mg/kg) and xylazine (0.02 mg/kg) coadministration to weanling bulls at the time of castration. Coadministration of xylazine and butorphanol resulted in reduced chute activity and clinical sedation characterized by muscle relaxation and occasional (<15%–20%) difficulty in exiting the chute. Cortisol concentrations immediately after castration were not evaluated in this study. However, treated calves were found to have significantly higher cortisol concentrations at 3 days after castration compared with castrated controls. The investigators concluded that butorphanol and xylazine did not reduce stress or improve performance.

α-2 Adrenergic Agonists

Caulkett and others described the used of xylazine hydrochloride as an epidural injection to provide analgesia at the time of castration.[64] Xylazine (0.07 mg/kg) was diluted in 0.9% sodium chloride to a volume of 7.5 mL, which was administered by caudal epidural injection.[61] In this experiment, 30 $\pm$ 14 minutes elapsed from the time of injection to castration in the 77 animals on trial. The investigators observed that 97% of animals demonstrated some degree of sedation with 2.6% of animals showing profound depression. In 80.5% of cases, the animal showed no response to surgical stimulation after epidural anesthesia. Only 14.3% of animals showed moderate ataxia after anesthesia; severe ataxia was observed in 2.6% of animals.

The technique for caudal epidural anesthesia has been described elsewhere.[52] Briefly, the location for epidural anesthesia is identified by lowering the tail and palpating the depression and movement between the respective vertebrae (**Fig. 7**). The overlying skin is disinfected and an 18 gauge needle measuring 3.57 to 5 cm is inserted in the center of the C1-C2 joint space while the needle is directed ventrocranially at an angle of 10° to vertical; essentially perpendicular to the general contour of the tail. The needle is inserted until it contacts the floor of the vertebral canal at which time it is withdrawn approximately 0.5 cm to avoid injection into the intervertebral disc. The correct placement of the needle is confirmed by observing a droplet of anesthetic in the hub of the needle being aspirated once the needle punctures the epidural space (the hanging drop technique). In addition, minimal resistance is encountered on the plunger of the syringe during the injection procedure when the needle is located in the epidural space. A dose of 1 mL of 2% lidocaine hydrochloride per 100 kg bodyweight provides local anesthesia of the perineum after 5 to 20 minutes and the effect lasts for 30 to 150 minutes.[52] Complications from caudal epidural anesthesia are rare and are most often associated with infection or injury if the animal becomes recumbent on a slippery surface.[52]

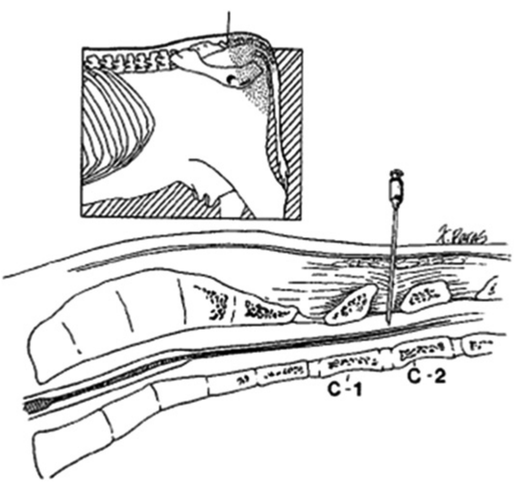

Fig. 7. Needle placement for caudal epidural analgesia in cattle. (*From* Skarda RT. Techniques of local analgesia in ruminants and swine. Vet Clin North Am Food Anim Pract 1986;2:621–63; with permission.)

Ting and colleagues[59] found that peak plasma cortisol concentrations were not significantly attenuated in calves administered a combination of 0.05 mg/kg xylazine and 0.4 mg/kg lidocaine epidural before burdizzo clamp castration. However, the integrated cortisol response (AUEC) was 26.5% less than in untreated calves (P<.05) (see **Table 1**). González and colleagues[10] observed that salivary cortisol concentrations were 60% lower at 4 hours after band castration in calves receiving xylazine epidural and flunixin meglumine (1.1 mg/kg) compared with castrated controls. Coetzee and colleagues[65] found that xylazine alone at 0.05 mg/kg IV or in combination with ketamine at 0.1 mg/kg reduced peak plasma cortisol concentrations by 8% compared with surgically castrated control calves. However, the integrated cortisol response was higher in treated calves compared with untreated controls. These data suggest a rebound in plasma cortisol concentrations once the effect of the drug wears off. Similar findings were reported in calves receiving a combination of xylazine, ketamine, and butorphanol before concurrent dehorning and castration in calves.[24]

N-Methyl-D-Aspartate Receptor Antagonists

Coetzee and colleagues[65] found that ketamine administered at 0.1 mg/kg in combination with xylazine at 0.05 mg/kg IV reduced peak plasma cortisol concentrations by 8% compared with surgically castrated control calves. However, the integrated cortisol response (AUEC) tended to be higher in treated calves compared with untreated controls. In this study, the half-life of xylazine and ketamine after IV administration was approximately 11 minutes. This result suggests that plasma cortisol concentrations likely rebounded in treated calves after the sedative-analgesic effect of the drug diminished. In this study, higher plasma norketamine concentrations were associated with lower plasma substance P concentrations compared with lower norketamine concentrations (**Fig. 8**).

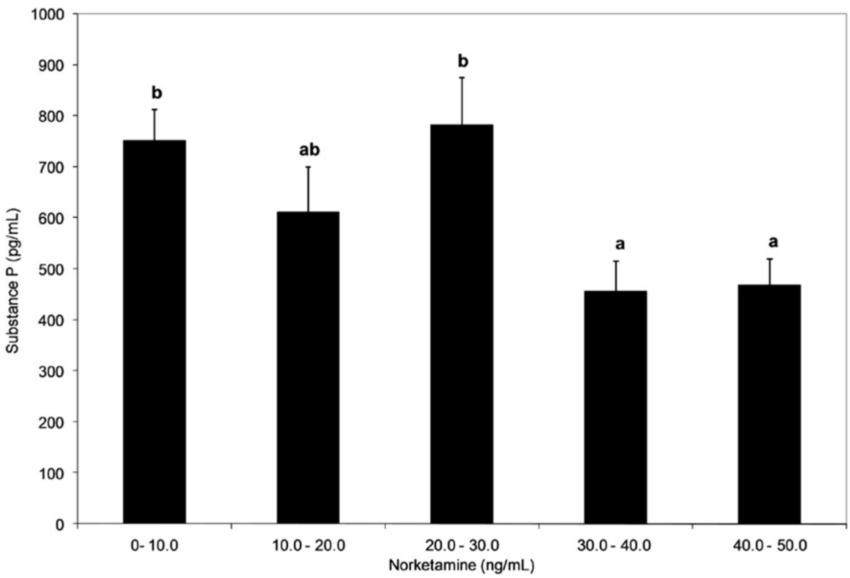

Fig. 8. Comparison between plasma substance P concentrations (pg/mL) and plasma norketamine concentrations (ng/mL) in calves receiving 0.1 mg/kg of ketamine before surgical castration. Columns with different letters are significantly different (P<.05).

SUMMARY

Castration of cattle is considered necessary to reduce aggression, prevent injuries in confinement operations, and to improve meat quality. However, all methods of castration have been shown to produce physiologic, neuroendocrine, and behavioral changes indicating pain and distress. Direct and indirect measurement of these changes using accelerometers, videography, HRV determination, electroencephalography, thermography, and plasma neuropeptide assessment may provide information that would lead to regulatory approval of analgesic drugs in livestock.

Administration of a local anesthetic alone effectively mitigates acute distress associated with castration but the integrated cortisol response is only modestly reduced. NSAID administration alone is not effective in reducing acute distress associated with castration, however the reduction in overall AUEC reported is greater in NSAID-treated calves compared with calves receiving only local anesthesia. The combination of local anesthesia and an NSAID achieved the greatest reduction in cortisol response in published reports, suggesting that a multimodal analgesic approach is more effective in mitigating the pain associated with castration than the use of a single analgesic agent. Lidocaine and flunixin meglumine are the only compounds with analgesic properties that are approved by the FDA for use in cattle. However, flunixin requires IV administration and at least once daily dosing to be effective. In the absence of compounds specifically licensed for pain relief in cattle, extra-label drug use regulations allow for unapproved analgesic drugs to be administered by or under the supervision of a veterinarian provided such use does not result in a violative tissue residue. Accordingly, a combination of local anesthesia with oral administration of a long-acting NSAID such as meloxicam may provide the optimum balance of convenience and analgesic efficacy at the time of castration.

Regulatory concerns combined with unease about the cost and convenience of drug administration at the time of castration is an impediment to the routine adoption of analgesic protocols in production systems. Although administration of multimodal analgesic protocols is associated with a significant decrease in plasma cortisol concentration after castration, most studies have not addressed the practical or production implications of these interventions in a commercial livestock environment, especially in beef cattle. Studies examining the health and performance effects of newer drugs with extended durations of activity are also needed. Regulatory approval of safe, cost-effective, and convenient analgesic compounds will support the implementation of practical pain management strategies as a part of standard industry practice at the time of castration.

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