Dechra

ANAESTHESIA & ANALGESIA

Multimodal pain management in cattle

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The definition of pain

Pain has been defined as *"an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage"*[1] in 1979. Since then, the knowledge and understanding surrounding the definition of pain have evolved.

Thus, an expanded definition of pain was published in 2016: *"Pain is a distressing experience with actual or potential tissue damage with sensory, emotional, cognitive, and social components."*[2]

In veterinary medicine, Molony and Kent defined pain as follows: *"Pain is an aversive sensory and emotional experience representing an awareness by the animal of damage or threat to the integrity of its tissues. It changes the animal's physiology and behaviour to reduce or avoid the damage, to reduce the likelihood of recurrence and to promote recovery."*[3]

Understanding and defining pain remains difficult due to the high subjectivity in the experience of pain. Especially in animals, which have no possibility of verbal communication, these definitions of pain can only be used to a limited extent.[4]

Methods for pain assessment in cattle

Cattle are stoic animals, inclined to flee from possible predators. Therefore, they attempt to mask and conceal signs of pain.[5] This behaviour has often led to the belief that cattle do not feel pain.[6] This makes the assessment and treatment of pain especially challenging in the bovine species.

Subjective and objective methods are available for assessing pain in cattle. A confounding issue with subjective pain assessment is that the evaluation of the state of pain that the animal is experiencing, always depends on the experience and assessment of the observer.[6]

Parameters for subjective pain assessment in cattle

Ethogram

An ethogram is used to observe and record the behaviour of an animal over a defined period of time.[7,8] Both posture and the frequency of certain behavioural patterns (e.g., head shaking) can be assessed.[8] Ethograms can reflect behavioural changes accurately[8] and have been used in numerous studies on pain assessment during castration or dehorning.

Numerical Rating Scale

In bovine medicine, the numerical rating scale is most often used in the context of surveys. A scale from 0 or 1 (no pain) to an endpoint of 10 (worst pain imaginable) is used to indicate how painful diseases or procedures are rated in cows and calves (Table 1).[5,9-11]

	Huxley et al.[5] (2006) n = 615	Laven et al.[11] (2009) n = 166	Remnant et al.[9] (2017) n = 242	Tschoner et al.[18] (2020) n = 274
Adult cattle				
Claw ulcer	6 (1 – 10)	4 (1 – 10)	7 (2 – 10)	7 (1 – 10)
Claw amputation	10 (2 – 10)	10 (5 – 10)	10 (8 – 10)	9 (5 – 10)
Caesarean section	9 (1 – 10)	9 (4 – 10)	9 (5 – 10)	9 (0 – 10)
Calves				
Castration (surgical)	6 (2 – 10)	8 (2 – 10)	7 (2 – 10)	9 (1 – 10)
Dehorning	7 (2 – 10)	8 (3 – 10)	7 (2 – 10)	8 (1 – 10)

Table 1: Assessment of painfulness of different procedures and treatments in adult cattle and calves (assuming no analgesia is administered) by veterinarians from different countries (median values, variance in parentheses).
The number of veterinarians participating in the surveys is given as n.

Pain face

The pain face in adult cattle was described in 2015 in the context of the publication of a pain scale for cattle.[12] For the evaluation of the pain face, four areas of the face (ears, eyes, facial muscles, and muzzle), whose expression changes when cattle are in pain, are assessed.

The ears may be tense and directed backwards or downwards ("lamb ears"). The eyes show a tense stare or a withdrawn appearance, eye and/or facial muscles are tense. The nostrils are often dilated and tense.[12]

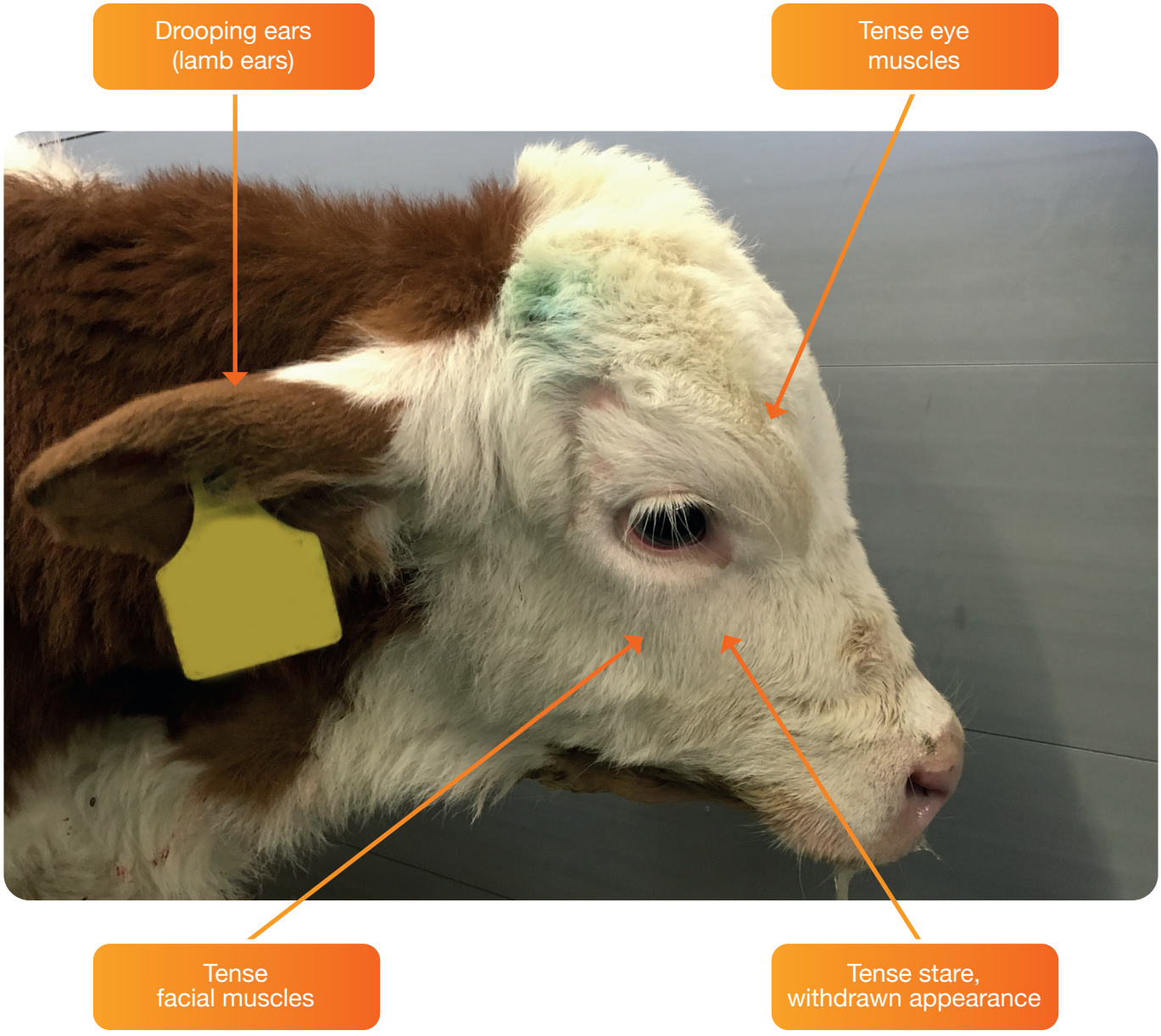

Figure 1: Painful expression on the face of a chronically ill calf as described by Gleerup et al. (2015). The ears are drooping, the gaze is tense and expressionless. Both eye and facial muscles are tense.
Source: Dr. T. Tschoner.

Parameters for objective pain assessment in cattle

Cortisol concentrations

Cortisol is a glucocorticoid and is produced in the adrenal cortex.[13] Cortisol is an indicator for stress associated with pain and has long been used as a pain indicator in cattle.[14]

However, cortisol concentrations in cattle are influenced not only by pain but also by environmental factors and management[15] as well as the specific behaviour of the individual animal.[16] Therefore, cortisol concentrations should always be assessed in combination with other parameters to distinguish between stress and pain-related distress.[17]

Substance P concentrations

Substance P is a neurotransmitter which is involved in the regulation of pain information and plays a role in the transmission of painful information to the brain.[18]

In a study dating from 2008, the authors found that substance P concentrations differed significantly between calves that were surgically castrated and calves that underwent the same manipulation but were not castrated (sham castration). In contrast, cortisol concentrations did not differ between the two groups.[17]

High variability of substance P concentrations between individual animals have been found[17,19] and basic research on the influence of specific stimuli on substance P concentrations in cattle is lacking.

Activity

Accelerometers can be used to record movements, activity, number of steps, and thus changes in animal behaviour.[20] Accelerometers are available in the form of pedometers, collars, or ear tags.[21] They can also be used for automated monitoring of cattle in loose housing systems.

Feeding and ruminating

Two well-known indicators of cattle wellbeing are feed intake and rumination. There is extensive research material using feeding and rumination time for pain assessment in cattle. There are several ways to record eating and rumination time, including using commercially available halters.

Eating and rumination time is negatively affected not only by pain, but also by stress and disease.[22]

Algometry

Algometry is used to measure the mechanical pressure an animal tolerates over a defined area (for example, after dehorning) before a defensive/evasive response by the animal occurs.

As an increase in local sensitivity (as can be seen in dehorned calves), is thought to result from pain algometry is used as an objective parameter for pain assessment.[23]

Multimodal pain management

In multimodal pain management, analgesics with different modes of action are used in combination. This prevents the development of pain in various parts of the pain system.

Multimodal pain management is recommended for routine zootechnical procedures (for example, dehorning), as well as for surgical procedures.[24] This technique always includes the combination of various components:

PRE-OPERATIVE ANALGESIA

Both NSAIDs and sedatives can be used as part of preoperative analgesia.

NSAIDs

Especially NSAIDs are used pre-emptively. This means that analgesics are administered in anticipation of a painful process rather than in response to the experience of pain.[25]

NSAIDs are organic acids without a steroid structure. **Inhibition of the cyclooxygenase 1 and 2 isoenzymes inhibits prostaglandin synthesis and thereby the development of pain and inflammation (Figure 2).**[6,24]

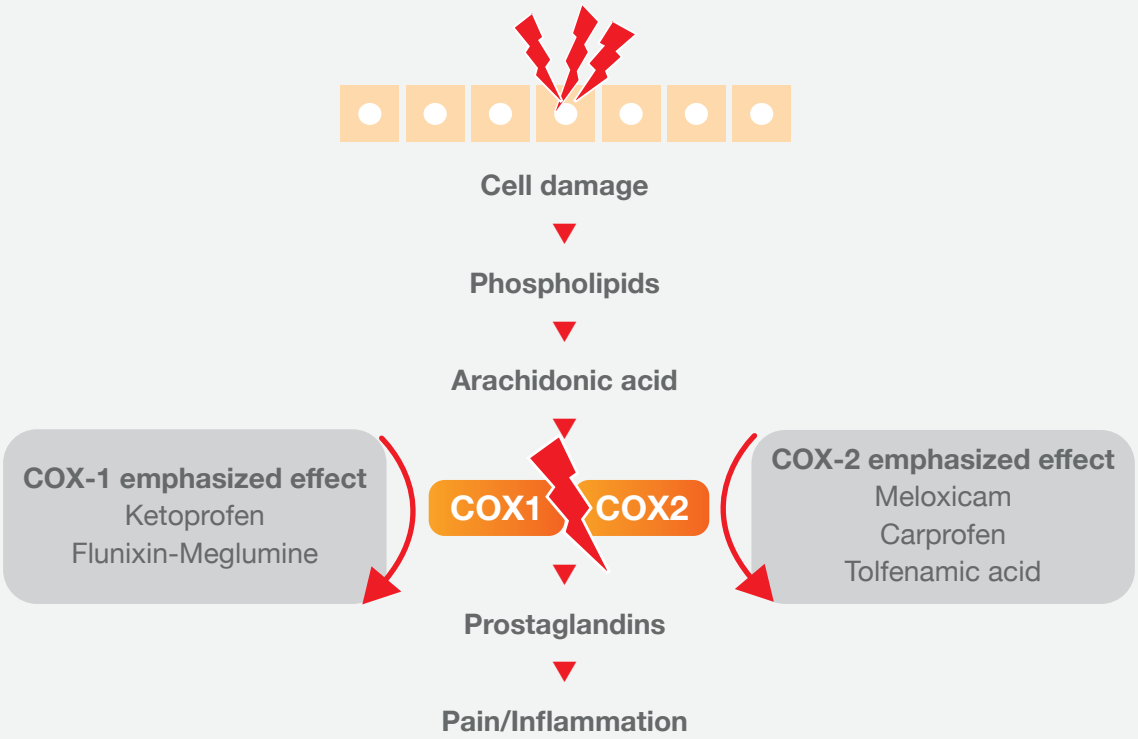

Figure 2: Mode of action of NSAIDS, adapted from Hudson et al. (2008) and Feist (2019). Use of NSAIDs results in the inhibition of the cyclooxygenase 1 and 2 isoenzymes, thereby inhibiting prostaglandin synthesis. As a result, there is a reduction in pain and signs of inflammation. Most NSAIDs approved in bovine medicine preferentially inhibit either COX-1 or COX-2.

Meloxicam

Meloxicam is an NSAID of the oxicam group with peripheral analgesic, antiphlogistic, and antipyretic effects. It exhibits COX-2 emphasized action without inhibiting the physiological functions of prostaglandin.

- Olson et al. (2016) found that calves administered meloxicam (1 mg/kg BW, orally) two hours prior to surgical castration (without local anaesthesia) had significantly lower cortisol and substance P concentrations and significantly more lying bouts than calves treated with only a placebo.[20]

- Substance P concentrations in calves are 0.5 times less after intravenous administration of meloxicam (0.5 mg/kg BW) immediately before dehorning, compared with a control group.[26]

Ketoprofen

Ketoprofen is an arylpropionic acid derivative (based on carboxalic acid) and is one of the new generation NSAIDs.[27] Ketoprofen has analgesic, antiphlogistic, and antipyretic effects. After intravenous administration in cattle, the half-life is 2.1 hours.

- Cows treated with ketoprofen (3 mg/kg BW, intravenously) for 3 consecutive days following claw surgery showed significantly better weight bearing by the fourth day post-surgery, than animals receiving a placebo. In addition, ketoprofen-treated animals were significantly more alert to their environment.
  In the first 24 hours after surgery, a significantly higher number of placebo-treated animals exhibited drooping or backward facing ears, as well as vocalization and teeth grinding.[28]

- In cows with digital dermatitis, administration of ketoprofen (3 mg/kg BW, intramuscularly) in combination with a local antibiotic resulted in a 2.57-fold lower likelihood of still being lame one week after treatment, compared with a control group treated with only a local antibiotic.[29]

Flunixin-Meglumine

Flunixin is mainly used in veterinary medicine as a salt in combination with meglumine. It's mode of action is a COX-1 emphasized inhibition of cycloxygenases. In addition to the antipyretic and antiphlogistic effects, the analgesic component is dominant in this agent. The half-life in cattle is 4 to 8 hours depending on the route of administration.

- Calves undergoing surgical castration without local anaesthesia which were treated with flunixin-meglumine (3.33 mg/kg BW, Pour-On) showed significantly lower cortisol concentrations up to 4 hours after castration compared with calves that did not receive analgesic treatment.[30]

Metamizole sodium

Metamizole is a pyrazolone derivative of the group of antipyretic non-opioid analgesics. Therefore, it does not belong to the NSAIDs. Metamizole appears to have peripheral and central analgesic effects, but the mechanisms are unclear. In addition to opioid-like analgesia, metamizole has antipyretic and antiphlogistic properties.

Metamizole has a spasmolytic effect (especially in the gastrointestinal tract), without resulting in a paralytic impairment of peristalsis. The half-life in humans is reported to be 3 to 5 hours.

- In a group of calves receiving a combination of meloxicam (0.5 mg/kg BW, intravenously) and metamizole (40 mg/kg BW, intravenously) before surgical correction of an uncomplicated umbilical hernia under isoflurane anaesthesia, substance P concentrations were lower at all time points during and after surgery compared with a control group receiving meloxicam alone.[31]

Sedation

Another important aspect of pre-operative analgesia is sedation. The following agents can be used:

Xylazine and Detomidine

Xylazine and detomidine are α2-adrenoceptor agonists resulting in sedation and analgesia by inhibiting the release of substance P, norepinephrine and in muscle relaxation.

Both agents act on the central and peripheral autonomic nervous systems and inhibit the sympathetic nervous system.

The sedative effect sets in approximately 10 to 15 minutes after intramuscular administration. The half-life of xylazine is 30 to 36 minutes, the analgesic effect lasts about 20 minutes, and the sedative effect lasts up to 4 hours. Ruminants respond more sensitive to xylazine administration than other animal species.

Detomidine has a higher selectivity for α2-receptors, resulting in a longer duration of its effects. Because of this higher selectivity, detomidine can be used in highly pregnant cattle as well since it has no effect on the uterus.

- In 2012, Rizk et al. showed that cows that were administered xylazine (0.05 mg/kg BW, intramuscularly) before being placed in lateral recumbency for functional claw trimming had significantly lower cortisol concentrations while being in lateral recumbency than cows that received a placebo.[32]

- During endoscopic abomasopexy as described by Janowitz, cortisol concentrations in cows treated with xylazine (0.02 mg/kg BW, intravenously) 15 minutes before the first skin incision were lower at all time points during surgery compared with control than in animals, which were treated with a placebo.[19]

The results of these studies confirm that xylazine leads to a reduction of stress in cows in the context of multimodal pain management.

PERI-OPERATIVE ANALGESIA

Peri-operative analgesia includes local anaesthesia. In Germany, procaine hydrochloride (with or without a vasoconstrictor) is the only local anaesthetic approved for cattle. The administration of procaine hydrochloride results in a reversible and local decrease of the membrane permeability for cations. This means that pain impulses are not transmitted and thus do not reach the brain - pain perception does not occur. Addition of vasoconstrictors delays the absorption of the local anaesthetic and prolongs its effect.

However, local anaesthetics combined with vasoconstrictors must never be used in an area with end arteries (for example, on the claw), as this might lead to necrosis of the tissue. All of the local anaesthesias presented in the following are used after shearing the respective area and aseptic preparation.

Local anaesthesia in the flank

For local anaesthesia in the flank, two techniques, paravertebral nerve block and line block can be used.

- Proximal and distal paravertebral nerve block desensitize the dorsal and ventral nerve roots (or rami) of spinal nerves. The nerve branches of the thirteenth thoracic and the first two lumbar vertebrae are blocked.

The advantage of paravertebral anaesthesia is that it also anaesthetizes the peritoneum. Depending on the number of administration sites, 60 to 80 mL (proximal paravertebral nerve block) or 90 mL (distal paravertebral nerve block) of a 2% procaine hydrochloride solution are used. For proximal paravertebral nerve block, locate the craniolateral end of the transverse process of the third lumbar vertebra. Puncture from the midline of the back through the dorsal longissimus muscle and the intertransverse ligament and administer a 15 mL procaine hydrochloride depot at a depth of 5 to 7 centimetres. A further 5 mL is administered above the intertransverse ligament as the cannula is withdrawn. The same procedure should be followed for the second and first lumbar vertebrae.[33]

- For distal paravertebral nerve block, 15 mL of 2% procaine hydrochloride is distributed in a fan shape parallel above and below the transverse process of the third to the first lumbar vertebra. In addition, a line block (30 to 40 mL of 2% procaine hydrochloride) can be administered parallel to the last rib to anaesthetise branches of the 12th thoracic nerve.[33]

- Line block involves infiltration of the subcutaneous tissue and deeper layers. A laparotomy requires between 150 and 200 mL of a 2% procaine hydrochloride solution for a 25-cm-long incision in a cow. After pre-piercing a hole with a cannula, the subcutaneous and deeper tissue layers are infiltrated with a 14-cm-long cannula. For this, the cannula is inserted and the local anaesthetic is administered while withdrawing the cannula.[33] As an increase in local sensitivity (as can be seen in dehorned calves), is thought to result from pain algometry is used as an objective parameter for pain assessment.[33]

The effect of the above local anaesthesia techniques occurs after 10 to 15 minutes, and lasts for about 90 minutes.[33]

Local anaesthesia in the limb

Intravenous regional anaesthesia is often used for procedures and surgeries in the claw because it is an easy way to eliminate pain. A rubber tourniquet (Esmarchschlauch) is placed on the affected limb proximal to the metacarpus or metatarsus.

The congestion causes the superficial toe veins to protrude. Using a 1.1-mm-thick and 30-mm-long cannula, puncture one of the superficial toe veins (common dorsal digital vein III, common plantar digital vein II or IV, Figure 3).[34]

After allowing some blood to escape through the cannula, inject (without prior aspiration) 20 to 25 mL of a 2% procaine hydrochloride solution WITHOUT a vasoconstrictor agent. The tourniquet should be removed after 90 minutes.[34]

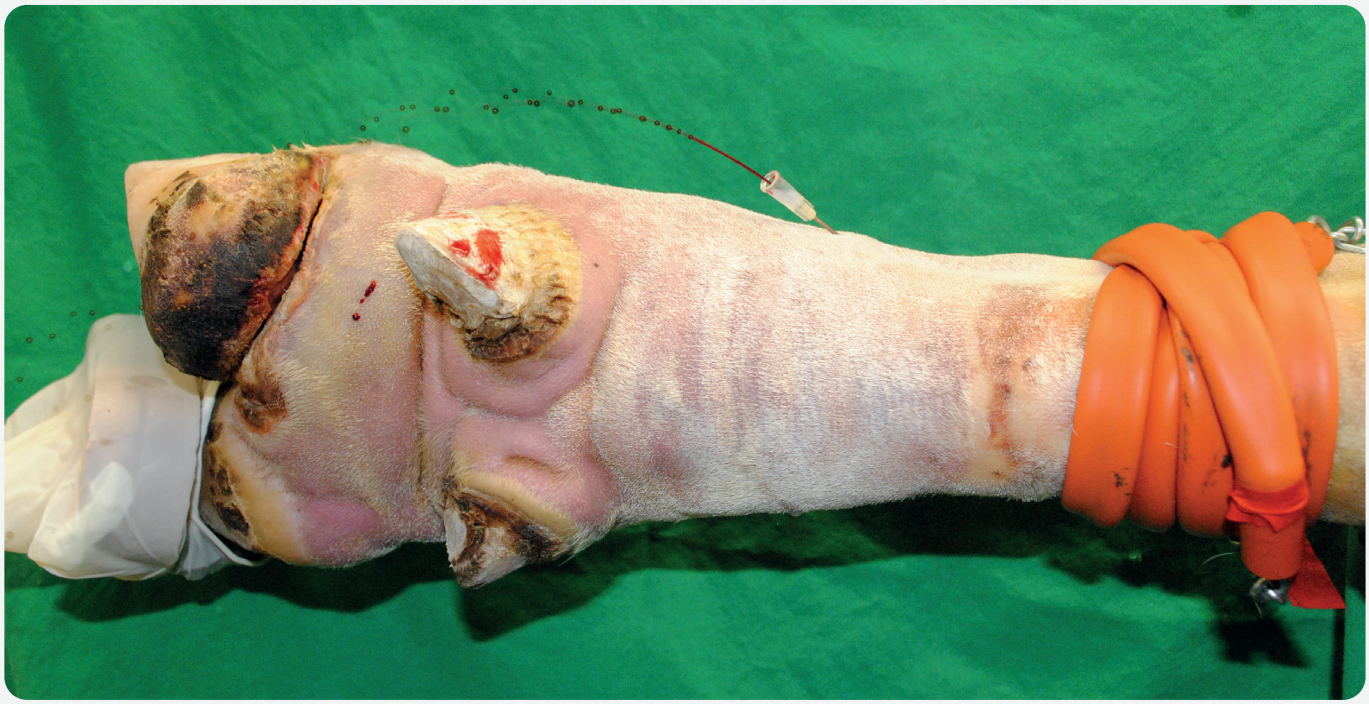

Figure 3: Intravenous regional anaesthesia on the hind limb of a Simmental cow. After applying a rubber tourniquet (Esmarchschlauch), a superficial toe vein is punctured and 20 to 25 mL of a 2% procaine hydrochloride solution is injected. Source: Dr. T. Tschoner

Local anaesthesia for dehorning

For dehorning or removal of horns, the cornual nerve, a branch of the zygomatic temporal nerve (part of the trigeminal nerve) is anaesthetized.

The localization for the local anaesthesia injection is midway between the lateral corner of the eye and the base of the horn. A depot of 10 mL of a 2% procaine hydrochloride solution is injected below the lateral end of the frontal crest at a depth of 2 centimeters.[33,35] It is recommended to place another depot (5 to 10 mL of a 2% procaine hydrochloride solution) caudally to the base of the horn.[33]

The combination of local anaesthesia, sedation, and the administration of an NSAID is considered the gold standard both in calves less than six weeks old as well as in older calves.[24]

Local anaesthesia in the teat

Different local anaesthetics can be administered in the teat.

- The **ring block** is often used in teat surgeries. For this, a 25G needle is used to inject 5 mL of a local anaesthetic directly into the muscles and skin around the base of the teat.[36]
- For surgery of the mucosa of the teat, 10 mL of a **local anaesthetic can be administered into the teat** cistern after milking out the teat and creating a blood-milk barrier (for example, using a tourniquet). Subsequently, the local anaesthetic is milked out again. This method of anaesthesia does not anesthetise the muscles and skin of the teat.[36]
- For **intravenous anaesthesia** at the teat, any superficial vein can be punctured and 5 to 7 mL of a local anaesthetic injected after creating a blood-milk barrier.

POST-OPERATIVE ANALGESIA

- For post-surgery operative analgesia, administration of an **NSAID is recommended for several days**.
- In addition, the cattle should be kept in a **sick pen**.
- After claw surgery, a bandage is applied, and a orthopaedic plastic shoe or wooden block is glued to the unaffected claw to provide relief.[24]

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We would like to thank Dr. med. vet. Theresa Tschoner (specialist veterinarian for cattle and Dip. ECBHM) for providing the technical content and for collaboration.

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