

Pain Relief for Livestock Husbandry Procedures

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A livestock pain relief innovation in Australia in 2005 that led to an awakening of on-farm pain welfare management, was the development of a 'spray and stay' topical anaesthesia and antiseptic wound formulation (topical anaesthetic formulation (TAF); Tri-Solfen[®], Medical Ethics, Australia) for use during mulesing in sheep. This product, when applied to wounds, rapidly alleviates pain through blockage of nociception, ablates hyperalgesia, minimises bleeding and provides antisepsis with reduced need for antimicrobial cover during healing. With a rapid onset and prolonged duration, the readily observable clinical efficacy commenced a transformational 'welfare revolution' in Australian livestock agricultural attitudes and practices with over 120million animals now treated. On application, the TAF forms a long-lasting bio-compatible barrier over the wound, creating its own intrinsic analgesic properties and diminishing the risk of biofilm formation. The TAF acts as a slow-release carrier for the actives, including the two local anaesthetics, lidocaine hydrochloride (5% w/w) and bupivacaine hydrochloride (0.5% w/w), the antiseptic cetrimide (0.5% w/w), in addition to the vasoconstrictor adrenaline acid tartrate (0.00451% w/w) that minimise vasodilation and bleeding, preventing systemic absorption and risk of toxicity. The TAF keeps the actives in contact with the wound tissue, creating synergies that prolong the analgesia well beyond the expected duration of action of actives (at least 24 h) and hastening both healing of husbandry wounds and other lesions, especially those induced by epidermal viral infections including Foot-and-Mouth Disease virus.

Keywords: cattle ; buffalo ; sheep ; goats ; pigs ; pain management

1. Pain Relief for Livestock Husbandry Procedures

The combined application of the topical anaesthetic formulation (TAF) delivered directly onto the wound peri-operatively or immediately postoperatively, with or without oral or parenteral non-steroidal anti-inflammatory drug (NSAID), was immediately recognised to have broader applications in livestock husbandry than mulesing. Numerous trials involving several routine aversive husbandry procedures have demonstrated the TAF to be safe and efficacious in managing pain and improving healing of acute surgical wounds incurred during: (i) surgical castration and tail docking of lambs; (ii) surgical castration and disbudding/dehorning of calves; and (iii) surgical castration of piglets ^{[1][2][3][4][5][6][7][8][9][10][11][12][13][14][15][16][17][18][19][20][21][22][23][24]}. The TAF has also been demonstrated to be effective in managing disorders with chronic wounds and lesions. A study in dairy cattle undergoing debridement of hoof abscess involving treatment with TAF reported significant reductions in pain during the procedure, with reduced post-surgical lameness ^{[9][25][26]}. The TAF has also been used for improving wound management in a range of situations, including: shearing cuts in sheep; lameness caused by hoof injuries and abscesses in sheep; open wounds in horses, dogs, cats and other companion animals and wildlife; and, most recently, for superficial vesicular, ulcerative and erosive lesions resulting from viral infectious diseases of the epidermis, with potential for reductions in viral loads post-therapy ^{[27][28]}. Consistent findings from these studies include regular producer confirmation of rapid onset of wound analgesia, positive welfare outcomes for an extended period well beyond that expected when the duration of action of the anaesthetic actives is considered and likelihood of improved pain management when used with an NSAID. Occasionally, there has been evidence of improved livestock productivity, mostly demonstrable in weaned animals ^[23].

2. Mulesing for Myiasis Management

Myiasis (flystrike) is one of the most serious causes of morbidity and mortality in Australian sheep. The TAF was registered for widespread commercial use in 2012 in Australia to manage the pain and hasten the healing of open wounds incurred during mulesing in mostly Merino wool sheep that are at high risk of flystrike due to the presence of 'breach wrinkle', the conformation that readily retains urine and faeces and provides an attractive environment for deposition of the eggs of the sheep blowfly *Lucilia cuprina*. Following hatching, the blowfly larvae burrow into perineal tissues and the lower back, causing penetrating wounds. The afflicted animal soon becomes moribund and untreated cases usually die. Whilst long-term breeding programs for fly-resistant sheep is occurring, the mulesing procedure to create a smooth scar of unwrinkled

skin of the breech and tail remnants remains the most effective method to provide life-time protection against flystrike [1][4][5][8].

The rapid adoption of TAF during mulesing performed by registered mulesing contractors and farmers in Australia has enabled the sale of wool classified as 'PR' (pain relief) and has improved welfare of sheep susceptible to flystrike, during the extended period required until genetic alterations in Australian Merino sheep phenotypes can progress sufficiently to successfully reduce the risk of breech myiasis. It is estimated that over 120 million lambs have now been safely treated with TAF since product registration. Importantly, plasma local anaesthetic levels have been shown to be well below toxic thresholds, even when relatively large doses were applied (up to 50 mg/kg lidocaine) in lambs. Following field reports that lambs appeared far more amenable to being moved after surgery when treated with the TAF, trials measuring wound pain and healing rates, including systematic behavioural assessments, quantitative sensory testing of wounds with von Frey monofilaments or algometry and wound photography technology established that effective wound analgesia occurred for at least 24 h, with improved wound healing [1][4][5][8].

3. Tail Docking and Castration in Lambs

Amputation of the tail in livestock or tail docking is a routine husbandry procedure in sheep production globally, for prevention of myiasis and improved fertility [7]. Tail docking causes acute pain in lambs, although is often performed without pain relief, despite increasing demands that the practice should be avoided or at least include pain management [1][6][7]. Tail docking practices vary between regions and countries, involving either rapid amputation by surgical excision or, more commonly, application of a rubber ring causing ischaemia that eventually leads to delayed removal of the necrotic tissue by sloughing. There is clear clinical evidence that the initial application of the ring causes extreme pain and close examination of animals in the period prior to sloughing of the necrotic tail remnant indicates there is also a high likelihood of pain from the chronic inflammation that occurs under and just proximal to the ring until the tissue is removed, sometimes several weeks after ring application. Estimates from the UK indicate that >90% of farmers remove tails from lambs, with rubber rings most commonly used (86%), followed by surgical (3%) and other methods (2%) [6]. Tail docking by surgery involves severing the tail using a sharp knife, scalpel, a hot knife or docking iron to cauterise the wound; it is considered a far less painful method to the use of rings on tails without application of local anaesthesia [1][2][6][7]. When surgical tail docking with and without general anaesthesia (GA) was compared, with and without inclusion of wound therapy with TAF, it was found that the TAF provided superior pain relief, improved healing, reduced wound infections, reduced cortisol responses and avoided elevation of serum amyloid A [6]. It was concluded that surgical tail docking without GA but where wounds were immediately sprayed with TAF was an affordable and more welfare-appropriate method for conducting tail docking in lambs [6].

In surgical castration of lambs, when the TAF was sprayed onto the spermatic cords and cut edges of the scrotum, lambs displayed reduced pain-related behaviour and sensory testing confirmed that hyperalgesia of the wounds was attenuated [1][2][10]. The use of local anaesthesia with NSAIDs, as a multimodal pain relief strategy for livestock undergoing routine husbandry procedures, is now recommended as best practice with recognition it provides greater amelioration of the pain response than use of a single agent alone [1][2]. Although several NSAIDs have been investigated, the use of meloxicam, available by veterinary prescription as a subcutaneous (SC) or intramuscular (IM) injection (Metacam® Boehringer Ingelheim, Germany) or via oral trans mucosal (OTM) application (Ilium Buccalgesic OTM®, Troy Laboratories, Australia), has been most advocated. As the use of elastrator bands to cause ischaemic necrosis of the tail and scrotal tissues of lambs in Australia is favoured by many producers, an instrument to enable intravenous administration of lignocaine to the neck of the scrotum or tail, prior to application of the band(s), has also been shown to reduce pain avoidance behaviours post-procedure (Numnuts®, Senesino Pty Ltd., Grange, Australia) [1][2][15]. The prolonged localised inflammation within the vicinity of the elastrator ring that occurs with this technique suggests that if it is to be promulgated as a preferred option for sheep producers, then use of an NSAID should also be recommended [1][2][16].

4. Castration and Disbudding/Dehorning in Calves

In extensive cattle productive systems in Australia, most husbandry interventions, including castration and disbudding/dehorning, are performed by producers [1]. This limits the use of veterinary prescription drugs, including anaesthetics and sedatives, due to administration safety and residue considerations described above. The TAF is now increasingly a preferred pain relief product for castration on beef cattle farms, sprayed directly into the scrotum peri-operatively, with reduced postoperative pain from attenuation of hyperalgesia for at least 24 h [1][2][29]. The NSAID meloxicam is also now becoming more widely adopted by cattle producers and is available by veterinary prescription for SC or IM injection or OTM application [1][26][30], with potential for prolonged availability when consumed in medicated molasses blocks (unpublished). Meloxicam has anti-inflammatory, analgesic and anti-pyretic properties, reducing

inflammation and pain-associated behaviours in castrated cattle ^[16]. Meloxicam is preferred over other NSAIDs for its prolonged half-life that extends duration of action to up to 72 h. The localised pain relief occurs from inhibition of cyclooxygenase (COX)-2 expression, reducing synthesis of the pro-inflammatory mediator, prostaglandin, which intensifies pain sensation and augments inflammation ^{[17][18][19][20][21]}. The use of TAF accompanied by intramuscular injections of an NSAID, administered by beef farmers under veterinary advice for disbudding and dehorning (with castration in males), appears to be rapidly increasing in northern Australian beef herd management ^[1]. The inclusion of an NSAID with the TAF in the pain-management protocols for this intervention is appropriate due to the risk of haemorrhage that may compromise adherence of the TAF to the disbudding/dehorning wound ^[21] and the potential for productivity improvements with this multimodal approach ^{[22][23][24]}.

Despite the extent of duration of action of meloxicam, the pain and inflammation resulting from both surgical and ischaemic castration is prolonged, with complete healing occurring between 4 and 9 weeks post-castration ^{[27][28][31][32][33]}. As the delivery of currently available pain relief products is impractical for managing this prolonged recovery period, an alternative delivery system has been proposed, using an NSAID incorporated into a feed supplement (e.g., pellets or molasses block). The administration of NSAIDs via a feeding system has the advantage that it removes the need for animal restraint to enable administration, with the therapy consumed prior to surgical procedures then continued in the recovery period for as long as deemed necessary. The NSAID flunixin meglumine delivered via medicated pellets successfully enabled therapeutic concentrations to be established within 6 h of consumption ^[34]. Currently, pharmacokinetic studies (unpublished) with incorporation of meloxicam into medicated molasses blocks appear to also successfully extend the availability and duration of action of this therapeutic (D. Van Der Saag, pers. comm.) and potentially offers a convenient method of extensively prolonging pain relief post-procedure.

5. Castration in Piglets

Amelioration of the pain of castration in piglets is an important global animal welfare issue. A trial with administration of the TAF spray into castration wounds demonstrated significantly lower wound sensitivity responses for up to 4 h, compared to those castrated following intra-testicular lignocaine injection or those with no treatment ^[35]. A further study assessed graded nociceptive resistance movements and piglet vocal responses in addition to mechanical sensory stimulation of the wound following castration. The conclusion was that the TAF administered immediately post-skin incision followed by a minimum 30 s wait period achieved highly significant pain mitigation during castration and in the early hours following the procedure ^[36]. These studies demonstrate that significant pain control is achieved with the TAF during the time periods associated with maximum pain in piglets undergoing castration, providing a practical and affordable method of improving piglet welfare ^{[35][36]}. There is also potential for a multimodal approach to pain mitigation in piglets ^[36]. Despite these findings, challenges remain in satisfying the various and extensive animal experimentation requirements for regulatory approvals ^[37]. Further, uncertainties of trials meeting both the ethical obligations to minimise the number of animals needed and the agreed optimal outcome variables to be measured to validate pain mitigation, have led to continuation of delays in progressing the animal welfare gains that would follow from widespread use of this approach for piglet castration ^[37].

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