Review of digital anatomy, infectious causes of lameness, and regional intravenous perfusion in cattle

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Abstract

Digital disorders in cattle constitute the majority of lameness issues that bovine practitioners will encounter. Treatment of many digital infections in cattle can be facilitated in part by regional limb perfusions of either local anesthetics, antibiotics, or both. This article reviews infectious causes of digital disease, relevant clinical anatomy, use of various perfusates and tourniquet types in regional intravenous perfusions in cattle, and potential complications associated with the procedure.

Key words: lameness, cattle, regional perfusion, local anesthesia

Résumé

Les problèmes digitaux chez les bovins représentent la majorité des cas de boiterie que les praticiens bovins vont rencontrer. Le traitement de plusieurs infections digitales chez les bovins peut être facilité par des perfusions régionales d'anesthésiques ou d'antibiotiques ou des deux dans les membres. Cet article passe en revue les causes infectieuses des maladies digitales, l'anatomie clinique pertinente, l'utilisation de plusieurs types de perfusats et de blocages dans les perfusions intraveineuses régionales chez les bovins et les complications potentielles associées à la procédure.

Introduction

Lameness in cattle is of significant economic importance to both the beef and dairy cattle industries. In a recent review of lameness lesions in beef cattle, 86.7% of lameness originated in the digit;[92] expedient and cost effective methods facilitating diagnostics and/or treatment in this region are of great importance. Perhaps the most economical approach to providing analgesia treatment to this area involves regional intravenous perfusion. This involves administration of a medication (usually a local anesthetic or potentially an antimicrobial) into the vasculature of a portion of the limb that has been isolated from systemic circulation by application of a tourniquet.[120] Once the drug is infused, both concentration and pressure gradients are created that maximize drug diffusion from the intravascular space to the surrounding bone and soft tissue structures.[120] Regional intravenous perfusion of antimicrobials is sometimes used to treat severe digital infections.

Review of Clinical Anatomy of the Bovine Distal Limb

Cattle are even-toed ungulates and bear weight on 2 digits (the 3rd and 4th digit) on each limb; the medial digit (3rd digit) is the primary weight-bearing digit in the front limbs, and the lateral digit (4th digit) is the primary weight-bearing digit in the hind limbs. The coronary band is proximal to the

hoof wall. The junction between the hoof wall and the sole is the white line, which is a relatively soft structure and is therefore a potential site of bacterial invasion into soft tissue structures if widening or trauma occurs there. Weight should be borne on the heel, the abaxial hoof wall, to a lesser extent the white line, the adjacent 10 to 20 mm of sole, and on the axial hoof wall from the toe and caudally approximately 1/3 of the length of the sole.[9] The remainder of the axial surface of the claw should not be weight-bearing[9] and should have a concavity.[36] The axial groove extends in a proximal-palmar/plantar direction from this concavity. The digital cushion is a fibroelastic layer deep to the sole that consists of 3 parallel fat pads that run from the heel and distal to P3, and act as a shock absorber for the digit.[113] The axial and abaxial pads extend from the heel longitudinally and run cranially beyond the level of the flexor tubercle; the middle pad frequently ends at the apical end of the flexor tubercle.[113]

The bones of the distal limb include the fused 3rd and 4th metacarpal or metatarsal bones. Bones of the digit include the first phalanx (P1, or the long pastern), the second phalanx (P2 or the short pastern), and the third phalanx (P3 or the coffin bone) which has a medullary cavity (Figure 1). The dewclaws, which are the vestigial 2nd and 5th digits, have a keratinized covering and are rarely involved in cases of lameness.[25] Their presence and position are relevant to radiographic scrutiny of the digits. Two paired proximal sesamoids are present at the level of each proximal P1, at the level of metacarpo or metatarsophalangeal joint capsules which communicate in 98.9% of cattle.[39] The proximal interphalangeal joints (between P1 and P2) do not communicate. The distal sesamoid bone (navicular) is present at the level of the distal interphalangeal joint (DIPJ) in each digit and serves as a trochlea for the deep digital flexor tendon;[25] this bone has an associated navicular bursa that serves to protect the deep digital flexor tendon that runs palmar or plantar to it. The bursa is not known to communicate with
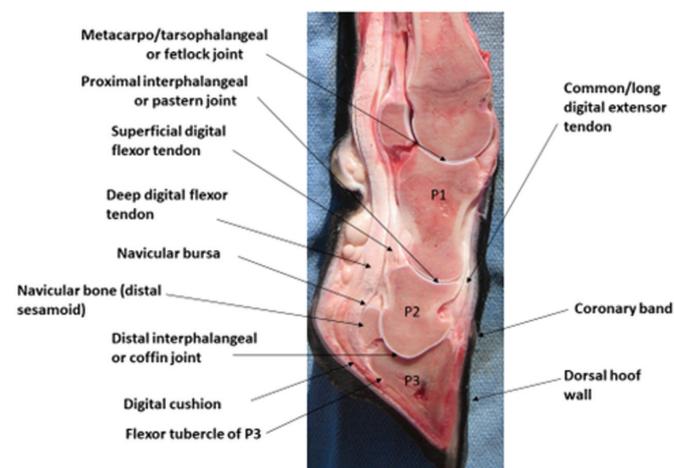

Figure 1. Bone, synovial, and tendinous structures of the bovine digit. Photo courtesy Dr. John Gilliam, Oklahoma State University.

the DIPJ. The ventral aspect of P3 has a flexor tubercle that the deep digital flexor attaches to; the superficial digital flexor attaches distally to P2. The flexor tubercle of P3 is the location distal to which sole ulcers may form if soft tissue inflammation, trauma, or poor biomechanics are present. The common (forelimb) or else long (hind limb) digital extensor tendons of digits 3 and 4 attach to the extensor process of P3. The interossei III and IV divide into 2 separate tendons proximal to the fetlock joint; these attach to the sesamoids and aid in supporting the fetlock joint along with the digital flexor tendons.[25] The digital flexor tendons are surrounded by the common digital flexor tendon (DFT) sheath, which may communicate proximally[36] in a small percentage of cases.[157] The tendons do communicate prior to bifurcation. The DFT sheath starts approximately 6 to 8 cm proximal to the proximal sesamoid bone in adult cattle;[36] it stops at the proximal level of the navicular bone. The proximal and distal (palmar or plantar) digital annular ligaments support the flexor tendons; the proximal and distal interdigital ligaments (cruciate ligaments) provide stability between the phalanges and also serve to support the flexor tendons. The proximal interdigital ligaments are attached on the axial surface of the proximal phalanges in the proximal half of that bone.[25] Digit amputations should not be performed more proximally than the distal attachment of the proximal interdigital (cruciate) ligament to avoid subluxation or luxation of the fetlock joint; a finger width below the dewclaws is generally a good landmark to use to determine the most proximal level that this can safely be performed. Important venous structures include the dorsal common digital vein III and the abaxial palmar or plantar digital vein III or IV, any of which could be accessed to administer a regional limb perfusion to the digit (Figures 2 and 3).

Infectious Causes of Digital Lameness in Cattle

In cattle, infectious digital disorders left untreated can result in local extension of the septic process to the phalanges, navicular bone, or synovial structures, collectively referred to as deep digital sepsis (DDS).[32,157,158] A variety of common causes of lameness may initiate this process; lacerations, sole ulcers, toe ulcers, white line disease, subsolar or retroarticular abscessation, penetrating foreign bodies, untreated or late-treated interdigital necrobacillosis, infected cracks in the hoof wall, or even iatrogenic or hematogenous inoculation of synovial structures can all result in infection and necrosis of essential weight-bearing digital structures.[11,23,32,48,58,88,129,134,143,149,158] Baggott et al reported that DDS was more common in dairy animals greater than 2 years, that had a large heartgirth, and were kept on pasture. Increased age was associated with increased incidence of digital sepsis.[11] In that same study, the heel and center of the sole were the originating sites of the majority of DDS.[11] Diagnostic modalities in such cases may include clinical examination, plain and contrast radiography, ultrasonography,
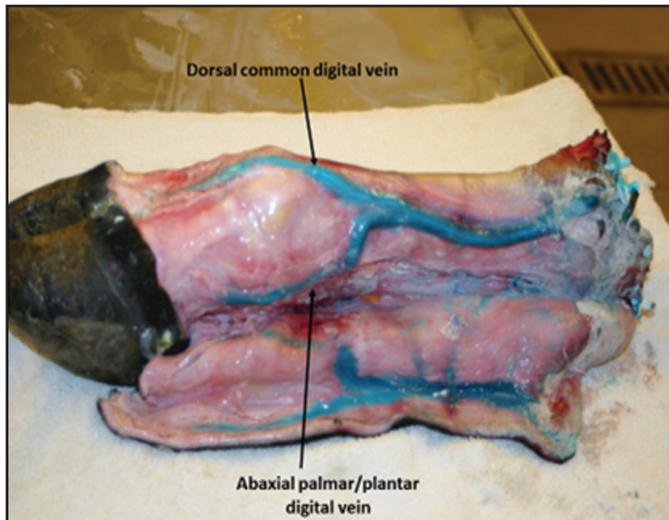
Figure 2. Veins utilized in RIVP of the bovine distal limb. Photo courtesy Dr. John Gilliam, Oklahoma State University.

Figure 3. 19 ga butterfly needle placement for RIVP in the dorsal common digital vein of the bovine distal limb. Photo courtesy Dr. John Gilliam, Oklahoma State University.

synovial centesis and cytologic exam, Gram stain and culture of affected structures, arthroscopy, tenoscopy, computed tomography, magnetic resonance imaging, and surgical exploration.[158]

Surgical treatment of DDS is warranted unless the animal is to be immediately slaughtered or humanely euthanized, and can involve local debridement, drainage, and lavage of affected structures, digit amputation, or facilitated ankylosis.[32,58,106] Medical therapy includes systemic and local antimicrobials, as well as appropriate pain management. Regional intravenous anesthesia or antimicrobial therapy could be utilized at least once during the course of treatment of DDS.

As numerous pedal disorders may result in deep digital sepsis, a variety of bacteria may be present in the lesion or lesions. This is particularly true if the region is open to environmental contamination.[58] Digital lesions in cattle are often associated with mixed bacterial infections, including synergism between Gram-negative anaerobes.[112] Bacterial pathogens associated with common digital diseases in bovine species include *Fusobacterium*, *Dichelobacter*, *Porphyromonas*, and *Prevotella (Bacteroides)* species, all of which are Gram-negative anaerobes.[17,112] Many of these organisms are normal inhabitants of the gastrointestinal tract in ruminants.[112] Additionally, *Trueperella* (previously *Corynebacterium, Actinomyces,* and *Arcanobacterium*) *pyogenes* reportedly has been recovered from over 80% of cases of deep digital sepsis.[158] Bacteria obtained from the pedal circulation in cattle with DDS included *Streptococcus* spp, *Trueperella pyogenes*, *Fusobacterium necrophorum*, *Escherichia coli*, and *Moraxella osloensis*.[131]

Hoof horn diseases, including sole ulcers and subsolar abscesses, accounted for the majority of hoof lesions on dairy farms in 1 study, when compared with digital dermatitis, other infectious diseases, and accidental lesions.[1] Sole ulcers in particular may be associated with infection of deeper osseous and synovial structures given their typical anatomic location at the heel-sole junction.[152] Deep septic pododermatitis has been associated with a poor prognosis for recovery.[81,108] However, aggressive surgical treatment can result in clinical cure and retention of the affected digit.[153] Toe tip necrosis syndrome has been documented and well-described in feedlot cattle, and pathogenesis is believed to include excessive wear along the apical white line resulting in bacterial invasion that can extend into the corium, possible toe abscesses, and sequelae including osteitis and necrosis of P3, osteomyelitis of P2, and ascending tenosynovitis.[64,65,101] Successful treatment has included removal of necrotic horn tissue to provide drainage, systemic antimicrobials and anti-inflammatories, and relocation to areas with earthen floors.[65]

Fusobacterium necrophorum is the predominant bacteria isolated in cases of interdigital necrobacillosis.[17] This disorder accounted for the majority of foot lameness cases treated by veterinarians in a study of British dairy cattle.[123] Additionally, saprophytic bacterial species capable of enhancing the inflammatory process can often be isolated in these lesions (*Bacteroides*, *Dichelobacter*, *Spirocheta*, *Staphylococcus*, *Streptococcus*, and *Bacillus*).[17,56] Synergistic activity between *Fusobacterium necrophorum* and *Trueperella pyogenes* resulting in DDS, with *T. pyogenes* being primarily responsible for the suppurative reaction, has also been reported.[69] Cases of interdigital necrobacillosis that extend to involve deeper structures have been reported to have a good prognosis with appropriate surgical intervention.[115]

In cattle, septic pedal osteitis or osteomyelitis most commonly occurs following bacterial invasion through the white line or the sole.[48] The disorder occurs sporadically in a herd, and has a higher incidence in cattle on concrete flooring.[37] Primary septic osteitis of the third phalanx without septic arthritis of the distal interphalangeal joint most frequently arises secondary to an untreated Rusterholz sole ulcer; these may progress to involve the deep flexor tendon as well.[158] Other causes of osteitis or osteomyelitis of the phalanges include foreign body penetration, extension of septic processes involving the laminae,[158] and toe ulcers

Treatment of pedal osteitis depends on the degree to which the third phalanx is affected.[48] If the lesion is amenable to curettage and removal of all infected and necrotic bone, complete recovery and retention of the affected digit is possible and prognosis is considered to be good.[37,48] Adjunctive therapy including systemic and local antimicrobials, pain management, and placement of a block on the sound digit to prevent weight-bearing by the affected digit, is warranted. If the septic process is extensive and localized resection of the affected regions not possible or economically feasible, digit amputation is warranted.[48]

Septic arthritis of the DIPJ occurs in 3 to 10.6% of deep digital infections,[97] and is more common in bovines than primary infection of that joint.[11] Very little physical barrier is provided by the soft tissues in this region, rendering this joint particularly susceptible to pathogenic invasion.[38,48] Sole ulceration, white line disease, and extension of interdigital necrobacillosis are reported to be the most common cause of septic arthritis of the distal interphalangeal joint in adult dairy cattle.[62] In a recent report in adult beef cattle, subsolar abscesses, penetrating wounds, and foot rot were most commonly associated with cases of septic DIPJ.[27] Deep foreign body penetration and septic vertical sandcracks originating at the coronary band may also result primarily in DIPJ sepsis.[158] Pathogens isolated from septic arthritis in the bovine digit have included *T. pyogenes*, *E. coli*, *F. necrophorum*, *Bacteroides*, and *Staphylococcus*.[12,37,38,53,61,69,79,80,145,164] In a study of bacteria from 75 cattle with articular sepsis, a high percentage of isolates were resistant to tetracyclines and sulfonamides *in vitro*.[96,145] Treatment of septic arthritis can be extremely challenging if the animal is to retain the affected digit. Conservative therapy includes systemic antimicrobials, anti-inflammatories, and pain management, but rarely effects a cure. More aggressive medical therapy involves joint lavage, either via distention or a through-and-through approach.[12,136,145,148] Placing a block on the sound digit is imperative. Surgical treatment includes arthrotomy, facilitated ankylosis, arthrodesis, or digit amputation.[19,37,38,57,61,84,97,106,145] Digit amputation can be performed utilizing a variety of different ways, but in a comparative study of 3 operative techniques amputation through the distal aspect of the first phalanx was preferable.[100] In a retrospective study of 85 cattle undergoing amputation of the digit, septic arthritis of the DIPJ was the most common indication for the procedure.[106] Likelihood of a good recovery was 71.4% in cattle weighing 750 lb (341 kg) or less, but decreased to 27.3% in cattle weighing 1500 lb (682 kg) or greater.[106] If bulls are to be retained for natural service, alternative surgical options, rather than amputation, should be explored.[57] Facilitated ankylosis resulted in a lower culling rate and faster return to milk production when compared to digit amputation in a study of Holstein cows,[20] and was reported to be 100% successful in returning affected cattle to productive use.[38]

Septic tenosynovitis of the digital flexor tendon sheath was reported in 4% of animals treated at a university refer-ral hospital;[77] the predominant tendon sheath affected was the lateral digital flexor tendon sheath of the hind limb.[137-142] Kofler reported that in 33 cattle with septic tenosynovitis, unilateral disease was present in 76% of cases.[78] *T. pyogenes* is the bacteria most commonly isolated in these cases.[5,143] *E. coli*, *Bacteroides*, *Proteus,* and *Bacteriacae* species have also been implicated.[5,6] Medical treatment includes parenteral and local antibiotics, anti-inflammatories, and block placement on the healthy digit, as well as repeated lavage of the tendon sheath which may be facilitated by use of indwelling multifenestrated drains; this has a reportedly good prognosis in cases of uncomplicated tenosynovitis.[5,6,143] Surgical treatment includes debridement, lavage, and drainage of the flexor tendon sheath either manually or via tenovaginoscopy, partial or full resection of the deep and/or superficial flexor tendons, or digit amputation.[5,6,18,57,106,143] Digit amputation in particular tends to result in decreased productive lifespan and possible failure to completely resolve the septic tenosynovitis.[5,106] Tenosynovitis, particularly when septic tendinitis or other synovial infection is also present, generally carries a guarded[6] to poor prognosis especially without aggressive therapy.

Sepsis of the navicular bone and bursa usually result from extension of infection from nearby structures. Osteitis or osteomyelitis of the region surrounding the flexor tubercle of the third phalanx is likely to result in septic bursitis and navicular osteomyelitis, particularly if the flexor tendon is involved.[158] Retroarticular abscessation may also result in navicular sepsis and bursitis.[158] Infection in these regions often results in additional septic processes of the middle phalanx and the flexor tendon sheath.[158]

In conclusion, a number of different insults may result in deep pedal infections, and therefore a wide variety of bacteria may be present in lesions of deep digital sepsis. Such bacteria may reflect the inciting cause of the initial lesion, secondary invaders, or environmental contamination in cases with open wounds or draining tracts.

Brief History of RIVP

Regional intravenous perfusion (RIVP), also known as regional limb perfusion (RLP), or intravenous regional anesthesia (IVRA), has been utilized extensively in both human and veterinary medicine for treatment of a variety of disorders.[72] The most commonly described perfusates are local anesthetics and antimicrobials, although chemotherapeutic agents have been utilized in human medicine and RIVP of antifungals has also been reported in the veterinary literature.[13,42] When local anesthetics are regionally perfused into a limb, the technique is often referred to as regional intravenous anesthesia, or the 'Bier block', named after the German surgeon who first described the procedure in 1908.[21] Since that time, regional anesthesia has been modified, well-described[7,16,43-47,68,74,88,89,110,135,147,159,161,164] and used extensively in large animal veterinary medicine, particularly in cattle but also in buffalo,[55,86,103] camels,[111] goats,[10] pigs,[135] and horses.[7,85]

Use of Local Anesthetics in RIVP

Although the concept was introduced in the human medical literature in the early 1900s, use of regional anesthesia did not become popular until the 1960s. In human literature, exsanguination of the limb is recommended prior to performing regional anesthesia; however, this has not been determined to be necessary in bovine veterinary medical practice. The local anesthetic most commonly used in IVRA of the distal limb of cattle is probably 2% lidocaine hydrochloride.[43]

Indications for regional intravenous anesthesia in cattle have included painful diagnostic procedures such as arthrocentesis, as well as treatment modalities including digit amputation, removal of interdigital fibromas, laceration, or local exploration and debridement of lesions, curettage of septic pedal infections,[160] facilitated ankylosis, and drainage and lavage of localized infectious processes including sub-solar or retroarticular abscesses.[43] Successful use of IVRA for tenorrhaphy in buffalo calves has also been described.[103] Additionally, IVRA can be used as a diagnostic tool to assist in the differentiation between lameness originating from the lower versus the upper limb.[129]

Regional anesthesia is particularly useful in ruminants given the inherent challenges of performing general anesthesia in these species, as well as the cost-effectiveness, convenience, and efficiency of the procedure by comparison.[47,68,150] Additionally, in comparison to both general anesthesia as well as other local nerve blocks[32] the number of injection sites is minimized, the procedure is rapidly accomplished, development of and recovery from analgesia is speedy, relatively small volumes of anesthetic are used, and advanced anatomic knowledge and technical skills are not required.[10] Furthermore, some control can be exerted over the duration of action of the local anesthetic.[156] Because of these factors, tissue trauma is minimized and risk of introducing contamination into surrounding tissue structures is similarly reduced.[46]

Regional perfusion also has advantages over peri-neural infiltration of local anesthetics in cattle. Deppe et al determined that regional intravenous administration of a local anesthetic resulted in complete, uniform, and more economic anesthesia than did ring block anesthesia of the bovine foot.[35] Additionally, hematoma and edema formation should not occur at the intended site of surgical manipulation as expected with local injection of anesthetic.[159] Local anesthetic injection directly at the site of a lesion may also fail to fully anesthetize the region due to poor diffusion from inflammatory processes,[68] as infection and inflammation tend to lower the pH of tissues and result in less ionization of local anesthetics into their tertiary basic and lipophilic form, which penetrates nerves.[15]

With RIVP of local anesthetics, onset of anesthesia is generally rapid and reportedly may be obtained within 5 to 10 minutes;[44,110] the authors have appreciated a more rapid clinical response, usually between 3 and 5 minutes. Volume of anesthetic injected also appears to affect the rapidity of diffusion into the distal tissues and the speed at which anesthesia is obtained,[43] as does location of the tourniquet. Conflicting reports exist as to the appropriate volume of anesthetic to use. Using 1.7% lidocaine hydrochloride with the tourniquet placed proximal to the carpus, Prentice et al found that at 10, 30 and greater than 30 mL of anesthetic, onset of anesthesia was apparent at 20, 10 to 15, and 5 minutes, respectively.[110] De Moore et al reported that reflexes could return prior to tourniquet release when only 10 mL of either 1% lidocaine or mepivacaine.[89] However, use of only 10 mL of bupivacaine hydrochloride in intravenous regional anesthesia distal to a tourniquet applied at the elbow of bull calves resulted in loss of reflexes and complete analgesia for the entire 90-min period of tourniquet application, suggesting a higher potency compared to other local anesthetics.[156] General recommendations in cattle have been that if the tourniquet is applied proximal to the tibiotarsal or carpal joints, 30 mL of 2% lidocaine is recommended whereas if the tourniquet is applied to the mid-metacarpus or metatarsus, 15 to 20 mL should be adequate.[43]

Concentration of local anesthetic does not appear to be critical to utility of IVRA.[68] However, onset of anesthesia was reportedly faster at higher concentrations of bupivacaine hydrochloride. When using equal volumes of 1% and 0.5% bupivacaine, complete anesthesia was seen at 6.8 minutes rather than 10.8 minutes, respectively.[156] Use of 4% rather than 2% procaine hydrochloride also resulted in more rapid onset of anesthesia with IVRA.[150] Manohar et al reported no difference in onset of anesthesia using 8 versus 10% procaine hydrochloride.[86]

Following RIVP with local anesthetics, recovery is also usually relatively rapid and typically occurs 5 to 10 minutes after the tourniquet is removed,[116] although partial anesthesia is reported for up to 75 minutes.[68,110] Following IVRA with 1% bupivacaine, weight bearing was not possible for an average of 43 minutes, and the calves were not ambulatory for an average of 70 minutes following release of the tourniquet.[156]

Failure of regional intravenous analgesia has been reported.[159] This has been attributed to a variety of factors, including inadequate tourniquet pressure, and failure of the anesthetic solution to diffuse uniformly from the vasculature into the surrounding tissues.[159] Following regional anesthesia of 40 bovine limbs, both thoracic and pelvic, 17.5% were classified as complete or partial failures.[110] These have been attributed to tourniquet slippage[116] or extravascular injection of lidocaine, although 7.5% of them were reportedly inexplicable.[110] Other authors have cited inadequate local anesthetic dose as a cause of regional intravenous anesthesia (RIA) failure.[89]

Although well-described in the human literature, conflicting opinions exist regarding the potential for local anesthetic toxicity following IVRA in cattle. Bogan et al reported that lidocaine administered via IVRA at 0.68 mg/lb (1.5 mg/kg) in healthy calves resulted in high concentrations distal to

the tourniquet, but fell markedly over 60 minutes. Systemic lidocaine concentrations during that time were low but measurable, and peaked within 5 minutes following tourniquet release but did not approach toxic levels.[24] The conclusion reached by those authors was that risk of lidocaine toxicity following IVRA in cattle was minimal.[24] Systemic lidocaine concentrations also peaked by 5 minutes post-tourniquet release, with no evidence of toxic effects, if dosed at 1.8 mg/lb (4 mg/kg) in an RIVP in otherwise healthy buffalo.[55] These authors determined that systemic lidocaine concentrations following IVRA in the hindlimb of healthy buffalo calves did not produce any clinically significant neurologic or cardiovascular changes before or after tourniquet release.[55]

Use of Antimicrobials in RIVP and Comparison to Systemic Administration

Regional intravenous perfusion of antimicrobials may offer some advantages over systemic antimicrobial administration in the treatment of DDS in cattle, including high drug concentrations at the infected site and low systemic drug exposure and potentially reduced residues.[60,66,117] Clinical use of antimicrobials administered via RIVP is often performed in cattle practice, but published reports describing the utility of this are scarce.[114] Studies on RIVP in the bovine using cefazolin, ceftiofur sodium, florfenicol, tetracycline HCl, ampicillin-sulbactam, and marbofloxacin have shown that antimicrobial levels in venous blood and synovial fluid in joints distal to the tourniquet can reach concentrations well above the MIC for common bacterial pathogens associated with DDS as well as other infectious agents of the bovine foot.[26,34,52,54,91,118] Additionally, a single RIVP of either marbofloxacin or ceftiofur sodium has been reported to result in effective clinical treatment of interdigital phlegmon in dairy cattle.[154] However, a single regional perfusion of 1000 mg of tetracycline hydrochloride was unsuccessful in resolving digital dermatitis in dairy cows.[118]

Some systemic antimicrobials have also been demonstrated to reach potentially therapeutic concentrations in synovial structures in the distal limb in cattle when administered parenterally. Florfenicol administered at 18 mg/lb (40 mg/kg) SQ was detectable in the metatarsophalangeal joint fluid at concentrations that exceeded the MIC_{90} for *F. necrophorum* and *B. melaninogenicus* for at least 6 days post injection; however, it did not exceed the published MIC for *T. pyogenes* (determined from uterine isolates).[67] Tulathromycin (at 1.25 mg/lb [2.5 mg/kg] SQ) and gamithromycin (3 mg/lb [6.6 mg/kg] SQ) were also detectable in synovial fluid at higher concentrations and for a longer duration than that of previously reported plasma values. For gamithromycin, data is not available to determine whether these levels were above the MIC for pedal pathogens, and tulathromycin was not detected at concentrations that exceeded the MIC_{50} of *F. necrophorum*.[67] Tetracycline HCl administered intravenously at 4.5 mg/lb (10 mg/kg) was detectable in tarsal synovial fluid at MICs higher than those for some digital pathogens for 8 hours; however, when administered as an RIVP (1000 mg per limb) synovial fluid concentrations remained higher than the MICs for the same pathogens for 24 hours.[118]

Use of many of the antimicrobials whose pharmacokinetics have been studied when used as an RIVP in cattle are currently prohibited for administration as a local perfusion in the US. In 1997, the FDA issued an order prohibiting the extra-label use of fluoroquinolones in food-producing species, and RIVP administration of any products from this class of drugs to a bovine would be illegal.[151] Similarly, in 2012 the FDA issued an order restricting the extra-label use of cephalosporins in cattle, swine, chickens, and turkeys. As there are currently no cephalosporins labeled for intravenous use in cattle, it would be illegal to use cephalosporins as an RIVP.[151] Additionally, tetracycline HCl must be compounded as an injectable in the US. Based on the Animal Medicinal Drug Use Clarification Act of 1994, it would be inappropriate to compound this drug for use as an RIVP unless no other drugs existed that could be used to treat the underlying condition. It is unknown if a similar dose of oxytetracycline (1000 mg) in 100 mg/mL formulation (labeled for intravenous use) would have a similar pharmacokinetic profile. Aminoglycosides have been extensively studied for use as an RIVP in horses, and from a pharmacologic standpoint use of such a concentration-dependent antimicrobial as an RIVP is ideal. However, the American Veterinary Medical Association and the American Association of Bovine Practitioners encourage members to avoid any extra-label use of aminoglycosides (including as an RIVP) in cattle due to the substantial risk for violative residues in food products associated with the prolonged elimination of aminoglycosides.[3,4]

Options for antimicrobials that are recommended to use for RIVP in US cattle, with scientific evidence that supports their use, are limited to florfenicol and ampicillin-sulbactam. Florfenicol is a broad spectrum antimicrobial, and displays concentration-dependent bactericidal activity against some bacterial pathogens (although these data are derived from respiratory pathogens). When given at a dose of 1.0 mg/lb (2.2 mg/kg) as an RIVP in adult cattle, it is likely (based on the pharmacokinetic profile and the probable pathogens involved) that it can be administered once per day in most clinical cases of digital sepsis.[54] However, clinical experience of the authors (KMS, RNS) suggests that phlebitis and/or venous thrombosis may occur with repeated RIVPs of florfenicol, thereby limiting the number of times an RIVP can be performed. Alternatively, ampicillin-sulbactam can be used at a dose of 1.5 g combined drug (1 gram ampicillin, 0.5 g sulbactam) in an adult bovine, reconstituted with as little as 3.2 mL of either sterile water or 0.9% sodium chloride. This dose should be proportionally decreased in smaller patients, such as calves. Although the label on 1 ampicillin-sulbactam product[a] indicates that it can be mixed with 2% lidocaine, the authors have noted that white discoloration of the drug consistent with precipitate formation often occurs

when lidocaine is used to reconstitute it. Based on the PK data obtained in one study,[34] a single daily RIVP of this drug combination may be effective in some cases of DDS. In cases in which precipitation of an antibiotic is known or suspected to occur when co-administered with lidocaine, a ring block or 4 point nerve block with lidocaine followed by RIVP with the selected antimicrobial may be indicated in order to allow both regional anesthesia and regional antimicrobials to be safely administered concurrently.

When repeated or daily RIVP of either antibiotics and/or anesthetics has been required, as in some cases of deep digital sepsis, the authors have placed an intravenous catheter in the dorsal common digital vein to facilitate RIVP. This has most often been an 18 ga, 2" catheter; occasionally use of a guidewire has been helpful in catheter placement. In cases in which long-term hospitalization and treatment were deemed necessary and economically feasible, longer term over-the-wire IV catheters have been used instead, including 8 French 20 cm catheters. A bandage was placed over the distal limb that protected the catheter insertion site. If catheter use is limited to once per day, the authors have instilled approximately 0.5 mL of undiluted heparin into the catheter in order to maintain patency if frequent flushing of the catheter with heparinized saline was not possible.

RIVP of antimicrobials has been used in other species as well, including horses and humans. Extensive studies describing various aspects of RIVP of antibiotics in equids have been published.[14,40,70,71,90,102,107,120-122] Of note is a recent report describing administration of a combination of amikacin and benzylpenicillin via RIVP in horses that resulted in synovial concentrations well above MIC for both drugs in the metacarpophalangeal joint for 24 hours.[33] One clinical study determined that minimal side effects were associated with RIVP of antimicrobials in horses, when compared to intraosseous perfusion.[121] However, complications including vasculitis have been reported with the use of enrofloxacin when administered into the vascular space.[102] Perhaps the most concerning complication reported in equids has been the association of regional antimicrobials for septic processes in the tibiotarsal joints with secondary septic foci in the limbs of foals.[125] Clinical signs consistent with septicemia following intravascular perfusion of the limb have similarly been documented in the human literature.[49] In one report, 4 out of 15 patients undergoing treatment for osteomyelitis developed signs of systemic sepsis within 4 hours following RIVP, and one patient was blood-culture positive, resulting in a recommendation that patients receive systemic antibiotics prior to institution of such therapy.[49]

Tourniquet Application in RIVP

Use of a tourniquet in regional perfusion of a limb with either local anesthetics or antibiotics has been described in both human and veterinary medicine, and also has application in the surgical realm to reduce blood loss and improve visualization of the surgical site.[22] Tourniquet use is described in a variety of veterinary species including horses,[120] cattle,[55,91] sheep,[128] dogs,[163] and cats.[82] In human medicine, advances in tourniquet instrumentation have included routine use of pneumatic tourniquets, as well as microcomputer-based tourniquet systems complete with audiovisual alarms in the event that hazardously high or low cuff pressures are present.[87,95]

Some types of tourniquets have been shown to be more effective than others when used in RIVPs in large animals. One study in cattle demonstrated that use of a pneumatic tourniquet set at 300 mmHg and applied proximal to the tarsus resulted in significantly higher levels of marbofloxacin in the tibiotarsal joint compared to those found when a wide rubber tourniquet (Esmarch tourniquet) was used.[26] Levine et al determined that in standing horses both pneumatic tourniquets and wide rubber (Esmarch) tourniquets achieved adequate concentrations of amikacin in the metacarpophalangeal joint when applied proximal to the carpus, but that narrow rubber tourniquets (1 cm) did not.[83] Alkabes et al demonstrated that in horses wide rubber (Esmarch) tourniquets were superior to pneumatic tourniquets when applied at the proximal metacarpus in preventing loss of amikacin from the vasculature distal to the tourniquet, and were also easier to use and less expensive than pneumatic tourniquets.[2] Plunkett et al determined that in standing sedated horses, a wide rubber (Esmarch) tourniquet applied at various levels on the limb reached and maintained the currently recommended subtourniquet pressures recommended for RIVP in equids (systemic blood pressure plus 100 mmHg) for 30 minutes.[109] Schoonover et al found that applying a pneumatic tourniquet above and a wide rubber tourniquet below the carpus prior to RIVP of low-volume amikacin resulted in higher concentrations of amikacin in the radiocarpal joint compared to placement of a single pneumatic tourniquet proximally.[126] Interestingly, exsanguination of the distal limb did not result in higher concentrations of amikacin in synovial fluid in that study.[126] Kilcoyne et al determined that there were no significant differences in synovial fluid concentrations of amikacin in the radiocarpal or metacarpophalangeal joints following RIVP with a single wide rubber tourniquet in place above the carpus for 10 versus 30 minutes; the conclusions of these authors were that 10 minutes of wide rubber tourniquet application could be sufficient for performing RIVP in standing sedated horses.[73]

A study of the pharmacokinetics of ampicillin-sulbactam when used as an RIVP in cattle utilized a wide rubber (Esmarch) tourniquet at the level of the proximal metatarsus and found adequate concentrations of both drugs in the synovial fluid of the metatarsophalangeal joint.[34] Rubber tourniquets also were used when determining the pharmacokinetics of ceftiofur sodium[91] and tetracycline HCl[118] when administered as regional limb perfusions in cattle; while studies investigating florfenicol[54] and cefazolin[52] for the same purpose utilized pneumatic tourniquets. Pneumatic tourniquets do not appear

to be practical or cost-effective for field use in cattle, and it is likely that an Esmarch or similar tourniquet (such as a wide rubber tourniquet cut from tire inner tubing), when applied appropriately, is adequate for performing RIVPs in clinical bovine practice. If such tourniquets are applied proximal to the tarsus in cattle, it may be of benefit to use 6" rolls of brown gauze or similar padding on either side of the calcaneal tendon attachments to ensure good venous occlusion. It is also important to note that there are inherent risks associated with tourniquet application regardless of tourniquet type used.

Tourniquet utility in medical and surgical procedures is due to ischemia and limited venous return.[75] Experimental studies in animals have shown that the blood flow to and from the limb distal to a tourniquet is less than 1% of the circulation of the unoccluded opposite limb.[75,76] The physiologic effects of tourniquet application also depend on the duration of and pressure applied by the tourniquet.[22] Similarly, complications related to tourniquet use increase as length of tourniquet time increases.[51,75,95] In humans it is recommended that pneumatic tourniquets not be left inflated for longer than 75 minutes.[119] However, in veterinary medicine conflicting reports exist regarding the appropriate length of time of tourniquet application. Following tourniquet placement to facilitate IVRA, clinical evidence of edema and lameness have been reported in a bull.[46] These were attributed to a tight tourniquet left in place for two hours and subsequent damage to lymphatic vessels.[46] However, clinically apparent detrimental effects were not obvious following tourniquet application for 2 hours in otherwise healthy cattle and sheep.[114] Most bovine procedures necessitating RIVP in the field would not be anticipated to take more than 2 hours, and therefore RIVP with a tourniquet in place for extended periods of time should not generally be a concern for practitioners.

Some of the adverse effects incurred by tourniquet placement have been attributed to alterations in the acid-base and tissue oxygenation status of the affected distal limb. Singh et al found that when a tourniquet is left in place for 90 minutes in cattle, significant acidosis and hypoxia occurs distal to the tourniquet; the authors therefore suggested that tourniquet application for that length of time may not be safe.[132] Chawla et al subsequently confirmed a local limb venous acidemia due to carbon dioxide accumulation following only 60 minutes of tourniquet ischemia in cattle; normal tissue oxygenation of distal limb tissues did not return for up to 150 minutes after release of the tourniquet.[28] The conclusion reached by these authors was that tourniquet application for even 60 minutes was unsafe.[28] Additionally, a decrease in pH distal to a tourniquet placed at the mid-metatarsus or metacarpus, from 7.4 down to 7.2, was apparent following regional anesthesia or antimicrobials in cattle.[144] However, a subsequent report suggested that in cattle, tourniquets could be safely applied for up to 90 minutes.[159] Following 120 minutes of pneumatic tourniquet application in horses, local venous acidemia, increased serum potassium, and apparently reduced hematocrit values were reported.[127] Considering the results of all of these studies, it would seem that in cattle tourniquet application for less than 60 minutes may be appropriate. Work in horses would suggest that tourniquet times of 30 minutes or less are adequate for RIVP of antimicrobials to achieve desired synovial fluid concentrations,[8,73] although this may vary depending upon the drug used.

Skeletal muscle injury following tourniquet application has been well-documented.[50] In a study involving rabbits, pneumatic tourniquet use at 350 mmHg of pressure for 2 hours resulted in decreased muscle function postoperatively; the quadriceps returned to 83% normal 3 weeks later.[104] Histologic evidence of muscle damage was found in a canine study, following 1-2 hours of compression at 350 mmHg.[63] Pedowitz et al demonstrated that rabbits with tourniquet application for 2 hours had marked histologic abnormalities with evidence of regional necrosis.[105] Elevations in creatine phosphokinase were present at 2 and 3 hours' duration of pneumatic tourniquet placement in another canine model.[29] Lack of evidence of skeletal muscle injury in cattle following tourniquet placement might be attributed to the relative lack of skeletal muscle in the distal limbs of cattle where the tourniquet is most frequently applied.

Tourniquet-related nerve injury has also remained a concern, even in human medicine.[95] Weingarden et al described peripheral nerve injury in a high percentage of limbs after tourniquet use, as evidenced by electromyography.[162] When mechanical tourniquets and higher tourniquet pressures were frequently used prior to widespread use of pneumatic tourniquets, 71% of patients with lower-extremity tourniquet application[41] and 77% of patients with upper-extremity tourniquet application[93] had evidence of denervation.[95] Nerve injuries reported following tourniquet use have ranged from a mild and transient loss of function to permanent and irreversible neuropathy.[95] Nitz et al noted progressive ultrastructural neuronal changes from 1-3 hours at 300 mmHg of tourniquet pressure in rats.[94] Studies have demonstrated that compressive neuropraxia, rather than ischemic neuropathy or myopathy, is the underlying cause of these injuries.[98,99] Nerve palsy apparently has not been reported if tourniquets are applied for less than an hour.[119]

Alterations in systemic blood pressure have been described following tourniquet application in anesthetized patients. Tourniquet-induced hypertension is defined as a 30% increase in systolic or diastolic arterial pressures following inflation or application of a tourniquet when compared to the first pressure recording following incision, and has been described in humans, horses,[30] and an ostrich.[31] However, detrimental clinical effects of increased systemic arterial pressures were not apparent.[30] Another study in equine thoracic limbs found that only reactive hyperemia was observed following tourniquet application for 30 minutes at 500 mmHg.[124]

Regardless of the underlying pathophysiologic mechanisms responsible for the tissue damage caused by tourniquet

placement, it is evident that length of tourniquet application should be minimized to the extent possible. In bovine practice, tourniquets are typically left in place for a maximum of 30 to 60 minutes for regional anesthesia or antimicrobial delivery.

Recognized Complications of RIVP

Compartment syndrome has not been reported in the veterinary literature following regional perfusion, but has been reported in the human literature. A report of 3 cases of compartment syndrome following regional anesthesia with lidocaine deemed the underlying cause in all cases to be incorrect dilution of lidocaine with hypertonic saline rather than isotonic saline.[59] Prentice et al reported an increase in creatine kinase levels 60 minutes following tourniquet release after regional analgesia in cattle, but control animals that received sedation and were cast into lateral recumbency showed similar increases and tissue damage due to IVRA was presumed to be negligible.[110] Hematological parameters were likewise unaltered during a 90-minute IVRA with bupivacaine hydrochloride in otherwise healthy bull calves.[155]

Some of the most severe complications associated with RIVP in cattle have included phlebitis and venous thrombosis distal to the tourniquet. One report stated that 2 cows out of 15 developed thrombosis of all veins distal to the tourniquet following RIVP with a combination of lidocaine and benzyl-penicillin, and concluded that direct toxicity had occurred because of an overdose of the antibiotic.[146] Another description of a cow that developed generalized distal limb venous thrombosis following 2 RIVPs, including 1 with both lidocaine and oxytetracycline credited the condition to multiple factors including endotoxemia from preexisting infection, RIVP, and tourniquet placement which can result in local ischemia, acidosis, and hypoxia.[81,133,144] Additionally, a report of caudal vena caval thrombosis in a Holstein cow suggested RIVP and treatment of DDS as being a potential source of bacteremia leading to sepsis and subsequent caval thrombosis.[130]

In 1 study, bacteremia was detectable in the pedal circulation in 5 of 10 cattle with DDS that underwent RIVP of 2% lidocaine followed by examination and/or debridement.[131] None of the control cattle (0/10) developed pedal bacteremia.[131] Based on this, the authors recommend either treatment with systemic antimicrobials prior to, or concurrent administration of antimicrobials via regional perfusion, at the time that RIVP of local anesthetics is performed in cattle with DDS to mitigate potential spread of infection to local or distant sites.

Conclusions

Regional limb perfusion of anesthetics or antimicrobials is an efficient and economical method of drug delivery to the distal limb in cattle, for a variety of lameness diagnostic and treatment purposes. It also results in lower systemic concentrations of drug, thereby minimizing drug residues in meat and milk. The procedure is generally considered to be safe and to have minor complications associated with it, although a few reports of catastrophic potential outcomes such as generalized distal limb thrombosis exist in the bovine literature. Use of a wide rubber tourniquet appropriately applied at a level immediately proximal to the region to be infused is likely to be effective in occluding venous return and allowing appropriate levels of perfusate to be delivered to the target area, which can also result in decreased risk of intraoperative bleeding during surgical procedures. The authors recommend that tourniquets not be left in place for more than 60 minutes to minimize the likelihood of complications associated with tourniquet placement. When attempting to use RIVP of 2% lidocaine to obtain regional anesthesia of the distal limb, 20 to 30 mL is likely to be effective in adult cattle if a tourniquet is applied at the mid-metacarpal or metatarsal region, but onset of anesthesia could be delayed, particularly in regions of deep infection or cellulitis. Local antimicrobials that have been demonstrated to reach potentially therapeutic concentrations for common pedal pathogens, and can also legally be administered via RIVP in cattle in the US following appropriate AMDUCA guidelines, include ampicillin-sulbactam and florfenicol. Florfenicol may be of some concern when administered via RIVP in cattle, as complications including phlebitis and venous thrombosis have anecdotally been reported. Careful consideration of amount of perfusate to be administered based on patient size and avoiding administration of a mixture of local anesthetics and antimicrobials that appear to have precipitated, is suggested (Table 1). Administration of broad spectrum systemic antimicrobials prior to performing RIVP with local anesthetics in cattle with DDS is highly recommended as bacteria may translocate into the vasculature and potentially spread infection to other sites.

Endnote

Acknowledgements

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Table 1. General recommendations for performing RIVP in US cattle.

General Recommendations for Performing Distal Limb RIVP in US Cattle
Good restraint of animal and complete restraint of affected limb
Wide (10 cm or greater) rubber tourniquet (such as Esmarch, or tire inner tubing cut to size) placed adjacent and proximal to affected region
Clip and aseptically prepare limb over vessel
Vasculature: dorsal common digital vein or abaxial palmar/plantar digital vein
19 ga ¾" needle with 12" tubing
Exsanguination of distal limb likely unnecessary
Tourniquet time of 60 minutes or less

Possible perfusates based on current evidence and authors' clinical experience:

Local anesthetic: 2% lidocaine. Effects last for ~10 minutes after tourniquet removed. Recommend administering systemic antibiotics prior to RIVP with lidocaine in cattle with known or suspected deep digital sepsis.
Adult cattle: recommend 20-30 mL if tourniquet placed on metacarpus/tarsus. Recommend 30-40 mL if tourniquet placed proximal to carpus/tarsus.
Calves: recommend 5-10 mL if tourniquet placed on metacarpus/tarsus. Recommend 20 mL if tourniquet placed proximal to carpus/tarsus. Consider diluting to 1% lidocaine in smaller patients.

Antimicrobials: florfenicol or ampicillin / ampici llin-sulbactam

Florfenicol: 2.2 mg/kg, 1-2 times maximum, 24-48 hours apart. Vasculitis noted if used repeatedly. Give directly off needle, do not administer mixed with any other substance.

Ampicillin / Ampicillin-sulbactam: 1.0 / 1.5 grams combined drug in adult cattle; proportionately lower dose in smaller patients. Appears to visibly precipitate with lidocaine, but authors have reconstituted drug with lidocaine and not appreciated obvious adverse effects upon administration. Can be given multiple times or through a catheter at 12-24 hour intervals.

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