How to Select Cases and Perform Field Technique for Regional Limb Perfusion

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1. Introduction

Vascular isolation of a limb, or part of a limb, through the use of a proximal tourniquet for isolated drug delivery to the distal limb, was first used in humans for regional anesthesia, commonly known as a Bier block, after August Bier. The technique of regional limb perfusion (RLP) for local antimicrobial delivery in horses was first described in 1990. Since 1990, equine RLP has been thoroughly investigated by several scientific publications and has become a part of routine equine practice. It is likely that RLP has found such great acceptance among equine practitioners largely because of the horse’s tendency for distal limb injury, the relatively dirty environment in which the horse lives, and the difficulty and expense of treating distal limb bacterial infections that can often be life- and/or career-threatening.

The most striking benefit of RLP is that high antimicrobial concentrations can be achieved in distal limb tissues, including synovial fluid, with a low antimicrobial dose (relative to systemic dose) and maintained above the minimum inhibitory concentration (MIC) for most organisms for up to and exceeding 24 hours. Other benefits include relative ease of the technique once learned, no need for specialized equipment, minimal invasiveness, minor significance of most complications, minimal patient resistance, and the limited time required to complete the procedure (approximately 40 minutes). In the author’s hospital, RLP is nearly a daily occurrence in the treatment or prevention of distal limb infection.

Mechanism

Antimicrobial drug delivery for most water-soluble, non–protein-bound drugs is a pressure and concentration gradient–dependent phenomenon, in which passive diffusion across a gradient occurs until equilibrium is reached. The equilibration rate is affected by the surface area to volume ratio (SA:V); whereas a high surface area (endothelium) to low volume (interstitial fluid) results in rapid equilibration to most tissues. This explains the apparent poor delivery to synovial structures where delivery is actually not inhibited but slow, due to a low SA:V ratio. In the joint, the surface area of the synovium is low relative to a high volume of synovial fluid volume (low SA:V ratio), resulting in delayed and probably reduced total drug delivery to the synovial fluid.

During RLP, equilibration to the tissues and the synovial fluid is enhanced in three ways: a change in pressure (1) and concentration (2) gradients and
by a mechanical effect (3) to the endothelium. A tourniquet-induced rise in blood pressure results in dilation of venous capillaries and post-capillary venules (but not the arterioles), causing widening of the gaps between endothelial cells and an increased pressure gradient, improving drug diffusion to all tissues. This is able to overcome slow synovial delivery (due to low SA:V ratio) for synovial fluid. Vascular isolation by the proximal tourniquet maintains a very high drug concentration within the vascular space of the limb. The high concentration and wide concentration gradient speeds tissue and synovial fluid equilibration to a much higher plasma drug concentration. One final mechanism, unrelated to the RLP technique itself, for successful maintenance of high intra-articular drug concentrations (after RLP or IA injection) is again the effect of SA:V ratio on equilibration down a concentration gradient. The low SA:V ratio (low surface area of synovium to high volume of plasma) delays drug clearance by equilibration, allowing maintenance of high drug levels within the synovial fluid for longer periods, compared with other distal limb tissues.

**Case Selection**

Clinical application of RLP is most often performed in the treatment and prevention of musculoskeletal infections, including infections involving bones, joints, tendon sheaths, foot tissues, and soft tissues of the distal limb. There is clear benefit of RLP over systemic antimicrobials alone in synovial infections, especially when tissues are too swollen for intra-articular injection or in tissues with reduced perfusion, such as blunt trauma or skin flaps, where improved drug delivery would be paramount to prevent and treat infection. Even when intra-articular injection is possible, the two techniques can be combined (with same antimicrobial for both routes) for added clinical benefit; intra-articular injection will result in significantly higher synovial concentrations, RLP will result in significantly high interstitial and soft tissue concentrations, and both techniques will contribute equally to very high bone concentrations (see Reference 19). Although not routine, use of RLP as a stand-alone therapy for antimicrobial administration, without systemic antimicrobials, has been successful in cases in which antimicrobials are avoided because of antimicrobial-associated diarrhea or expense. Most often however, RLP is used in combination with systemic antimicrobial treatment as well as surgical debridement, topical therapy, and joint lavage when required.

There have been a few reports of successful RLP in foals, and RLP has been successfully used in the author’s hospital in young foals (Figure 1). When RLP is used in the young foal, systemic antimicrobials should be always used concurrently to limit theoretical RLP-induced septicemia. If RLP with an aminoglycoside is elected in foals, it is critical to time RLP to coincide with administration of the systemic dose. Additionally, the RLP dose should be subtracted from the total body dose to derive the remaining drug dose to be given systemically. These measures are taken to avoid perturbing the normal drug trough levels, protecting against nephrotoxicity when using aminoglycosides.

**Technique**

Briefly, under heavy sedation, the vasculature of a limb is isolated through tourniquet application (proximal or proximal and distal tourniquets), so that perfusate (venous blood plus injected drug solution) leakage under the tourniquet to the systemic circulation is minimized. Distal to the tourniquet, an aseptically prepared vein is catheterized and antimicrobial solution is injected by slow infusion over 2 to 3 minutes. The site of venipuncture is wrapped to prevent extravasation of perfusate during RLP. The tourniquet is left in place and the patient is maintained in a stationary and sedated state for 25 to 30 minutes. After the perfusion period, the tourniquet is removed and the technique is repeated daily until local antimicrobial delivery is no longer required (Figure 2).

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**Fig. 1.** Photograph of tibiotarsal joint lavage via needles with concurrent RLP in a 1-week-old foal. Black arrows demonstrate tourniquet locations. There is an over-the-wire intravenous catheter placed in the medial metatarsal vein, from distal to proximal, for daily RLP. From days 1 to 4 of hospitalization, the foal received daily joint lavage via needles, and systemic and intra-articular antimicrobials were administered. There was minimal improvement in lameness, swelling, and joint cytology. On day 4, a methicillin-resistant *Staphylococcus aureus* was identified from the synovial fluid. Daily RLP with 100 mg of vancomycin q.s., 30 ml in saline, was added to the above treatments on day 5, needle lavage was discontinued on day 7, and daily RLP was continued until day 14 of hospitalization. The foal was discharged on day 17 without lameness or joint swelling.
Selection of Infusion Location (Saphenous/Cephalic or Palmar/Plantar Digital Vein)

Clip and Aseptically Prepare Vein

Peripheral veins rather than arteries are used in RLP for several reasons: The mechanical effect of RLP for improved drug delivery (see above) does not occur within arterioles, so there is no benefit of arterial catheterization; drug-induced toxic effects occur more frequently and with greater severity within the endothelium of arteries as compared with veins; and arterial catheterization is more difficult than venous catheterization because of vascular tone and vessel size.

Both cephalic/saphenous veins and palmar/plantar digital veins have been used in RLP. When the treated site is distal to the metacarpus/tarsus, use of palmar/plantar digital veins with metacarpal/tarsal tourniquet application should be used to achieve the greatest drug delivery. When the treated site is the level of the carpus/tarsus, the proximal tourniquet is placed along the mid-forearm/gaskin and a second tourniquet should be placed distal to the treated site to achieve the greatest drug delivery. When proximal tourniquet and catheter application are required for distal limb delivery or when a second distal tourni-
The most common orthopedic pathogens are *Escherichia coli* and members of the enterobacter family, which are often susceptible to amikacin; therefore, amikacin is most commonly used, with reported doses ranging from 250 mg to 2.5 grams, although a dose of at least 500 mg should be used. When *Pseudomonas* is suspected, ticarcillin (1 gram), with its increased anti-pseudomonal activity, is often used (Table 1).

**Tourniquet Selection**

Tourniquet width is inversely related to blood flow past the tourniquet and to the application pressure required to stop blood flow. Therefore, a wide tourniquet requires less pressure for the same effect. Although narrow rubber, wide rubber, and pneumatic tourniquets have all been reported for RLP, narrow rubber tourniquets are inadequate and only wide rubber or pneumatic tourniquets should be used. Wide, pneumatic tourniquets set to pressures of 300 to 500 mm Hg are less likely to allow perfusate to leak to systemic circulation compared with a wide rubber tourniquet, in which application pressure is more variable, and, once lost, will not be regained. Gauze rolls can be placed to improve venous compression of either the wide rubber or wide pneumatic tourniquet.

An Esmarch-type tourniquet can be used to exsanguinate the limb before proximal tourniquet application. This will reduce injection pressure and may reduce the chance for perfusate leakage to the systemic circulation.

**Antimicrobial Selection**

There are several things to consider in antimicrobial selection. Antimicrobial selection should be based on results of culture and sensitivity when available. The selected antimicrobial should be water-soluble. The antimicrobial is most often concentration-dependent because very high concentrations are achieved with RLP, but concentrations fall rapidly, allowing the greatest gain in efficacy with concentration versus time-dependent antimicrobials. Selection of highly protein-bound drugs (i.e., ceftiofur) may maintain higher concentrations for longer periods, allowing RLP to be performed less often with maintenance of drug concentrations above MIC.

Despite scientific reports on RLP with enrofloxacin, it and other antimicrobials that are potentially toxic to the vasculature should not be used. Combinations of antimicrobials should not be used unless they are confirmed to be efficacious experimentally. This is due to the high concentrations achieved within semi-closed spaces (limb perfusate, synovial fluid) that may increase drug interaction, leading to drug inactivation. This is especially important in the combination of aminoglycosides and beta-lactam antimicrobials.

In the absence of culture results, the most common orthopedic pathogens are *Escherichia coli* and members of the enterobacter family, which are often susceptible to amikacin; therefore, amikacin is most commonly used, with reported doses ranging from 250 mg to 2.5 grams, although a dose of at least 500 mg should be used. When *Pseudomonas* is suspected, ticarcillin (1 gram), with its increased anti-pseudomonal activity, is often used (Table 1).

**Sedate Horse**

**Apply Tourniquet(s)**

Early studies and clinical use of RLP were in anesthetized horses. This was in part due to the pain of tourniquet pressure and resultant systemic hypertension. Currently, most clinical application of RLP is performed in standing, sedated patients. Accordingly, more recent RLP studies have been performed in standing, sedated horses to more accurately mimic clinical use and have shown a mild reduction in peak drug delivery. This probably is due to increased patient movement. A recent study identified the utmost importance of adequate sedation and maintenance of a stationary patient during standing RLP. The authors found that patient limb movements, however slight, significantly reduced synovial drug concentrations, most likely caused by perfusate leakage to the systemic circulation under the tourniquet during limb movement. In this study, mean fetlock synovial amikacin concentration was 317 μg/ml in horses that did not move and 25 μg/ml in horses that did move.

**Catheter Selection and Use**

Butterfly, over-the-needle, or over-the-wire catheters can be used. Unless catheters will be maintained long term, butterfly catheters are most commonly used. When patients are particularly difficult for daily limb venipuncture, especially in the hind limbs, the author places over-the-wire catheters to ease procedure and minimize patient movement (Figure 3). In any case, smaller-gauge catheters (26 gauge) should be used because they cause less damage to the endothelium and encourage slow infusion, minimizing perfusate leakage past the tourniquet. Unless an Esmarch-type tourniquet is used to exsanguinate the limb before RLP (to minimize injection pressure and presumably reduce perfusate leakage past the catheter), catheters are usually placed immediately after tourniquet application. Every effort should be made to ensure accurate venipuncture on the first attempt because repeated attempts at venipuncture lead to significant perfusate extravasation to the subcutaneous space, minimizing effective drug delivery.

Catheters can be inserted in either proximal-to-distal or distal-to-proximal direction. One disadvantage of distal-to-proximal insertion is that if injection is performed too quickly, there may be increased perfusate leakage past the tourniquet. Ad-
The advantages of distal-to-proximal insertion include greater security of the butterfly needle tip within the vein when gravity is not flexing the injection tubing and reduced tendency of in situ catheters to kink due to normal blood flow between perfusions. When an over-the-wire or over-the-needle catheter is used, insertion in a distal-to-proximal direction may minimize difficulty during insertion due to the presence of venous valves.

As previously mentioned, drug infusion should be performed slowly, to minimize perfusate leakage past the tourniquet. The clinician should check frequently that the needle tip remains within the vein, keeping in mind that blood-tinged flashback can oc-
Fig. 3. Photographs of a 9-year-old Warmblood gelding presented for laceration to the right hind limb after limb entrapment through the stall wall. A. There is tissue loss, blunt tissue trauma, and exposed bone, and the proximal extent of the wound was immediately adjacent to the tarsometatarsal joint. After confirmation of lack of synovial involvement via joint distention, the wound was debrided with primary closure. B. Daily RLP with 2 grams of amikacin q.s. to 60 ml in saline was performed proximal to the bandage using a 23-gauge butterfly catheter for medial saphenous injection and tourniquet duration of 30 minutes for 6 days. C. A gauze bandage is placed over the venipuncture site after injection and butterfly removal to minimize extravasation of perfusate at the venipuncture site while the tourniquet is in place. D. Fifteen days after the initial injury, the wound is healing well and ready for suture removal. The wound continued to heal without boney sequestration, exuberant granulation tissue, or other complications, and the horse returned to performance (show hunter).
cur from within an extravasated hematoma. One group suggested that a larger-gauge, over-the-needle catheter allows aspiration of blood and more accurate differentiation between hematoma flashback and accurate catheter tip location.30

Tourniquet Duration After Infusion

RLP Frequency

Tourniquet duration is usually reported to be 25 to 30 minutes; however, RLP for up to 2 hours during surgical procedures has been performed by the author, without adverse effects. Whatever duration is used, it is important to keep the horse well sedated for the duration of RLP because movement significantly and adversely affects the effectiveness of RLP.

The optimal frequency of RLP for prevention and treatment of musculoskeletal infections is not known. Very high drug concentrations that are many times the MIC for most pathogens are achieved during RLP; however, the drug levels fall quickly once the tourniquet has been removed as the drug diffuses back along its concentration gradient, to the systemic circulation. Therefore, most often, RLP is performed daily. When RLP cannot be performed daily, there still may be substantial clinical benefit to RLP every second or third day, especially when using concentration-dependent antimicrobials. If RLP cannot be performed daily, systemic antimicrobials must be used. When repeated RLP cannot be performed, a single application of RLP may also be of substantial benefit; for example, when treating a laceration, RLP can be performed during tissue debridement or after laceration repair and during bandage application, resulting in immediate and high antimicrobial concentrations in the target tissues.

Complications

Daily venipuncture for RLP does not appear to be associated with serious adverse effects, although it has been noted that accurate and successful venipuncture gets progressively more difficult, most likely due to local inflammation.16,30 Topical application of 1% diclofenac has been used and was found to significantly reduce local inflammation,31 which may prolong the period that RLP can be performed. Intravenous catheters can also be left in place and may also prolong the period that RLP can be performed.30,32

2. Results

Regional limb perfusion is used almost daily in the author’s hospital for postoperative cases, wounds, foot surgery, and septic synovial structures and prophylactically during difficult fracture repair and arthrodesis. This local antimicrobial delivery technique has greatly improved prognoses, reduced costs, shortened recovery times, and turned previously hopeless cases into cases with positive outcomes. Remarkably, the only recognized complication is local, self-limiting inflammation at the site of venipuncture. One potentially unrecognized complication that should always be kept in mind during RLP is the importance of accurate vascular isolation. A poorly placed tourniquet of inadequate width and even the slightest patient movements can drastically reduce the effectiveness of the technique.

In the author’s hospital, heavy sedation, a wide rubber tourniquet in place for 25 to 30 minutes, a butterfly catheter for injection into an accessible vein, and a single antimicrobial q.s. to 60 ml in saline is the standard technique. The antimicrobial selection and dose depends on the size of the patient, tourniquet location, and clinical problem. Many cases receive RLP for more than 1 week, and occasional cases have received successful daily RLP for more than 3 weeks. The author has used indwelling, over-the-wire catheters in 12 cases for more than 1 week when, for behavioral reasons, horses would not easily tolerate repeated venipuncture. The only complication noted was catheter kinking; when catheters were placed from proximal to distal (away from the heart), the catheters occasionally turned around to point distal to proximal (toward the heart), kinking the catheter.

3. Conclusion

Intravenous RLP is a highly useful technique to the equine practitioner and should be used in conjunction with standard therapies (systemic antimicrobials, surgical debridement and lavage, local injection) when treating or preventing distal limb musculoskeletal infections.

References and Footnote


