



Treatment of Claw Lesions: Necessary or Not

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Abstract

Topical treatment of claw lesions is common practice in the United States. According to a recent US survey regarding treatment of claw lesions, topical treatments were applied by 59% of veterinarians and 53% of hoof trimmers. The medication used most frequently was the soluble powder form of tetracycline (Tet) or oxytetracycline (Oxytet); used by 48% of veterinarians and 81% of hoof trimmers. The second most common product varied by user group with copper sulfate (CS) for veterinarians and ichthammol ointment (a sulfurous, tarry compound with mild antiseptic properties used primarily as a drawing agent) for trimmers. These compounds, particularly Tet and CS, have properties which are considered to be potentially deleterious to the healing of lesions. Tetracyclines are known to cause significant tissue irritation when used parenterally, CS is corrosive to the skin and eyes and both compounds may be absorbed through cutaneous tissues and open lesions. Considering what is known about the pathogenesis of claw lesions and the process of wound healing, there is reason to believe that topical treatment may not be beneficial. Sole ulcers occur secondary to mechanical loading properties associated with claw horn overgrowth and metabolic conditions that weaken the suspensory apparatus of the third phalanx. Healing of claw lesions occurs by second intention; that is, lesions are not sutured but left open to heal by the process of granulation tissue formation, re-epithelization and contraction of the wound edges. Wound healing of open lesions by second intention generally requires additional time compared with lesions closed surgically (i.e. by first intention) because of the time needed to generate a sufficient volume of connective tissue to fill the defect. Since the epidermis provides an important barrier to infection, the risk of infection is higher while the wound is open, and this serves as the argument for the use of topical treatment of claw lesions. However, topical treatments with a low pH (e.g. Tet) or corrosive properties (e.g. CS) are believed to cause cellular toxicity which might interfere with epithelial cellular migration and proliferation in the early stages of wound healing. The result is granulation tissue formation and inhibited epithelization and wound contraction. A small study was conducted to assess the effect of topical treatment with Tet and CS on the rate of wound healing as determined by the presence of granulation tissue and evidence of re-epithelization at day 21 post treatment. Photos of lesions at day 21 were presented to 2 independent observers who scored the lesions for the visual presence of granulation tissue and evidence of re-epithelization. Based upon observer scores at day 21, lesions topically treated with oxytetracycline (Oxytet) or CS were more likely to have granulation tissue ($p > 0.0054$) and less likely to have evidence of re-epithelization ($p > 0.0553$). Although the number of observations was small, the data suggest that topical treatment with Oxytet or CS may delay wound healing.



Introduction

Our research group at Iowa State University was awarded a grant from the Hoof Trimmer's Association and American Association of Bovine Practitioners Research Foundation at the annual conference in September 2012. The title of the project was: "Topical Treatment of Claw Lesions in Dairy Cattle". The objectives of the study were three-fold: 1) to determine current claw lesion treatment practices used by trimmers and veterinarians, 2) to assess the effect of claw lesion treatment practices on the healing rate of claw lesions, and 3) to determine the potential for treatment to result in detectable residues in milk. The following is a summary of the study and our findings.

A 3-Part Study

Part 1 of our study was designed to document claw lesion treatment practices used by hoof trimmers and veterinarians with specific reference to method of corrective trimming used, topical treatments applied, use of wraps or bandages and foot blocks. Members from both the HTA and AABP were asked to complete an on-line survey of their foot care practices. Preliminary results of the survey were presented as an abstract and poster at the 46th Annual Conference of the Bovine Practitioners in Milwaukee, Wisconsin. An abstract of the results were also presented at the International Symposium and 9th International Conference on Lameness in Ruminants, in Bristol, United Kingdom, August 11-14, 2013. The full version of the survey was published as a peer-reviewed article in 10-12 May 2016, Tehran, Iran | 63

The Bovine Practitioner in 2014 (Kleinhenz et al, 2014).

Part 2 of our study was intended to determine if current treatment practices are beneficial or potentially detrimental to claw lesion healing rates. For cows to be enrolled in the trial, they were required to meet the following criteria: 1) lame cows with a sole ulcer or white line lesion which had caused exposure of the underlying corium (either by the consequence of the disease or corrective trimming) and 2) only cows with new lesions (no chronic lesions or cows with a history of claw disease). Reasoning for these criteria was based upon our trial objective which was to assess the length of time required for re-epithelialization of lesions.

A third component of the study was to assess the potential for topical treatment of claw lesions with either tetracycline or oxytetracycline to result in detectable residue. Survey results confirmed our hypothesis and affirmed the necessity to determine if detectable residues were possible following topical treatment with these drugs. While there are a couple of reports in the literature (Britt, JS, et al, 1999; Cramer, G, et al., 2014) on the detection of residue following topical treatment of digital dermatitis; there are none to date that describe residue detection in cows with claw lesions topically treated with these compounds.

Animals, Lesion Selection and Treatment Groups

Animals and Lesion Selection: Eighteen lactating Holstein and Jersey



cows from the Iowa State University (ISU) dairy diagnosed with uncomplicated sole ulcers or white line lesions were randomly enrolled into either a treatment (10) or control (8) group. Researchers attempted to enroll only those cows with new lesions since our thinking was that to enroll animals with chronic lesions might confound the results. Healing of long-standing lesions is often complicated by permanent damage to the corium which prevents normal healing.

Treatment Groups: Animals assigned to the treatment group received corrective trimming, the fitting of a claw block to the contralateral healthy claw and topical treatment as follows: cows assigned to the topical treatment groups received a topical application of 7.3 g of oxytetracycline HCl soluble powder (7) or topical copper sulfate (3) using a powdered formulation of copper sulfate. Oxytetracycline was chosen for study as our survey indicated that tetracycline or its derivatives were one of the most commonly used topical treatments on claw lesions. Copper sulfate was included since survey respondents reported that it was also commonly used, particularly in organic operations. All lesions were wrapped with a co-flex bandage following the application of topical treatments. Wraps were removed after 24 hours to assess lesions. No further treatment was applied.

Animals in the control group received corrective trimming, a wrap and a foot block applied to the contralateral healthy claw; but no topical treatment. Wraps were removed after 24 hours (at day 1) for lesion assessment procedures. No further topical

treatment or bandage was applied beyond the day 1 assessment.

Lesion Evaluation Procedures

Lesion Photos: Photo images of claw lesions were taken at the time of enrollment (i.e. day 0), day 1 and at the third evaluation occurring 21 days post treatment. On day 0, the day of treatment, the foot was trimmed and treated according to group assignment. A loose wrap was applied to all animals including those in the control group. On day 1 (24 hours after enrollment) the loose wrap was removed from all animals followed by gentle cleansing of the lesions with water to avoid disturbing raw corium tissues. Lesions were subsequently photographed and the cow was released with no further treatment or bandaging of the lesion. All cows were reexamined at day 21 to assess wound healing progress and photograph lesions. Photos were maintained in a database for future evaluation by 2 observers who were blinded to treatment group.

Assessment of drug residue in topically treated animals: Corrective trimming of claw lesions generally results in the exposure of raw corium tissues. To date, there have been no reports of the potential for antibiotic residue following topical treatment of claw lesions. In order to determine the likelihood of creating a detectable residue in blood or milk we collected blood and milk samples from 11 cows with topically treated claw lesions. Seven cows (Farm 1) were treated with oxytetracycline soluble powder (7.3 grams) and 4 (Farm 2) with 1 scoop (equivalent to 25.5 grams) of tetracycline soluble powder. Blood



and milk samples were collected pre and post-treatment as follows: oxytetracycline treated cows sampled 3X/day and the tetracycline treated cows were sampled 2X/day for 3 days post treatment. Serum and milk samples were frozen after collection and submitted to the Pharmacology Analytical Support Team (PhAST) at Iowa State University's College of Veterinary Medicine. Drug concentrations were quantified using liquid chromatography-mass spectrometry with a level of detection for the assays at 1 ng/ml. Lesion surface area (exposed corium) was also calculated using ImageJ software (available from National Institutes of Health).

Results

At the start of study we found several animals with lesions that met the requirements for enrollment; however over time fewer animals were presented with lesions fitting the study criteria. Investigators attribute part of this lack of suitable candidates for study to seasonal effects of lameness (higher incidence rates occur in the late summer and early fall) and high beef prices, which resulted in higher culling rates and thus fewer animals available for study. As a result only 18 animals were available for study.

Visual Assessment of Lesions: Photos of lesions from day 1 and day 21 were presented to 2 observers who were blinded as to treatment group. Each was asked to evaluate the lesions for the presence or evidence of inflammation, granulation tissue and re-epithelialization. As might be expected, there was no statistically significant difference in lesions at day 1 for any of the parameters assessed.

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Figure 1. Cow 7894 - Lesion on day 1 following treatment with 7.3 grams of oxytetracycline woluble powder.



Figure 2. Cow 7894 - Lesion with exuberant granulation tissue on day 21.

For the day 21 photo observation, evaluators were asked to determine if lesions had evidence of excessive granulation tissue formation or evidence of re-epithelialization. Based upon observer evaluation of the photos of lesions at day 21, lesions topically treated with oxytetracycline or copper sulfate were more likely to have granulation tissue ($p > 0.0054$) and less likely to have evidence of re-epithelialization ($p > 0.0553$). Although the number of observations is small, these data suggest that topical treatment with oxytetracycline or copper sulfate may delay wound healing.



We speculate that this increase in excessive granulation tissue formation negatively impacts healing rate and may increase susceptibility of these tissues to secondary infectious diseases such as digital dermatitis. Similar to proud flesh in equines, trimming or removal of exuberant granulation is necessary to promote healing. A smooth bed of healthy granulating tissue on lesion surfaces is desirable, but when the granulation process becomes excessive or exuberant, healing is likely to be delayed. This is supported by a previous report from van Amstel et al., who found that lesions observed to have a marked granulation tissue response were also slower to heal (i.e. form new epithelium). Topical steroids were observed to dampen the inflammatory response but also reduce neutrophil migration and the production of inflammatory mediators.

Assay for tetracycline/oxytetracycline residue in topically treated animals:

Results of assays for tetracycline in plasma demonstrated a C_{max} (maximum or peak concentration) of $4.78 + 2.82$ ng/ml; for milk C_{max} was $20.64 + 14.51$ ng/ml (recorded at the 3rd milking on day 2). C_{max} for oxytetracycline in plasma was $2.15 + 1.20$ ng/ml (recorded at 48 hrs. post topical application); for milk C_{max} was $20.81 + 19.90$ ng/ml (recorded at the 7th milking (milking 3X/day). Regulatory action for oxytetracycline and tetracycline are > 300 ppb, which is well above levels observed in this study; but all post treatment samples had detectable levels of drug.

It was also observed that lesions with larger surface areas tended to have higher log-transformed drug

concentrations in both plasma ($R^2 = 0.51$; $P = 0.03$) and milk ($R^2 = 0.44$; $P = 0.03$). One might conclude that while topical treatment with either tetracycline or oxytetracycline derivatives is likely to result in detectable residues, concentrations are well below actionable levels.

Discussion

Wound healing is a very complicated process usually described in terms of three (some do not include hemostasis) or four overlapping phases including hemostasis, inflammation, proliferation, and maturation. The primary objective is a rapid unimpeded re-epithelialization of the lesion. Research on the healing of claw lesions shows that depending upon severity and other complications, this process may require as little as 25 days or in complicated situations as much as 42-60 days. Lischer et al. (2001) evaluated healing rates on 74 cows with 105 claw lesions over a 6-month period. Their data indicated that the mean time for the formation of a closed layer of new epithelium was 25 days for lesions causing slight corium alterations, 33 days for moderate corium alterations, and 42 days for lesions causing severe alterations of the corium.

In this study claw lesions treated topically with oxytetracycline or copper sulfate were more likely to have excessive granulation tissue and less new epithelium at day 21 post treatment compared with non-treated controls. Topical medications used in the early stages of wound healing cause necrosis (i.e. death of tissues) that interferes with cellular migration and epithelial cell proliferation, key events in the wound healing process. Research on wound healing in equines has shown that topical treatment with



acidic compounds or agents with corrosive properties are capable of causing cellular toxicity. In fact, the equine literature lists a vast array of compounds (that are also commonly used in cattle) that are capable of adversely affecting wound healing including strong iodine, copper sulfate, tetracycline and its derivatives and other products (Auer and Stick, 2012). This information and the results of this study strongly suggest that if topical treatment is necessary, it needs to be accomplished with compounds that will not cause additional tissue damage or interference with wound healing.

This study is the first to report on the potential for drug residue from topical treatment of claw lesions. Although the levels of drug detected in both plasma and milk were well below regulatory limits for tetracycline, it is nonetheless important to know that absorption of the drug does occur following topical treatment of lesions. One might speculate that in small herd situations where many animals may receive topical treatment, sufficient absorption of the drug could occur to result in a violative residue.

Clinical observation of animals with claw lesions topically treated with tetracycline derivatives or copper sulfate (CS) suggest that these compounds cause significant irritation and pain in the immediate post-treatment period. To assess the possible effects of topical therapy with Oxytetracycline soluble powder (Oxytet) and CS on discomfort in the immediate post treatment period, a simple ethogram was developed to record behavioral indicators of pain. Primary behaviors monitored included: lifting of the foot or leg and toe touching (i.e. resistance to placing the foot firmly on the ground). Over a

period of 15 minutes in the immediate post treatment period we observed that cows treated with either Oxytet or CS exhibited nearly 3 times as many pain-related behaviors (mean of 4.5/15 min for cows with no topical treatment compared with a mean of 13.6/15 min. for cows treated with Tet or CS). We conclude that these compounds increase post treatment discomfort. Assuming topical treatments as used in this study appear to delay healing, could result in an antibiotic residue and seem to increase post treatment discomfort, we conclude there is little benefit to topical therapy of claw lesions.

In Summary,

Investigators would readily concede that this study has not yielded the definitive answer to the question of whether topical treatment procedures are beneficial or detrimental to the healing rates of claw lesions. Instead, our results on a limited number of animals suggest that topical therapy with tetracycline derivatives (and possibly copper sulfate) increases inflammation causing pain in the immediate post treatment period, a greater tendency for the formation of granulation tissue and reduced epithelialization of lesions (i.e. delayed healing). These data suggest that the objective of treatment should be to remove all necrotic tissue and undermined claw horn without causing damage to peripheral healthy tissues. This in combination with the application of a foot block to the healthy claw is sufficient in most cases to reduce discomfort and promote recovery of claw lesions. Consistent with previously published information, there does not appear to be any



advantage to topical treatment with either tetracycline or copper sulfate and a bandage or loose wrap. Finally, our study of cows with topically treated claw lesions using tetracycline derivatives confirms that such

treatment results in detectable residues in plasma and milk. Levels detected are well below actionable levels, but nonetheless significant.

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