

Comparison of topical lidocaine/prilocaine anesthetic cream and local infiltration of 2% lidocaine for episiopeplasty in mares

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Local anesthesia and tissue inflammation associated with lidocaine infiltration and lidocaine/prilocaine topical anesthetic cream for episiopeplasty in mares were compared. Twenty-two mares were randomly assigned to lidocaine or lidocaine/prilocaine topical anesthetic cream treatment groups. Perineum and vulva were cleaned, 8–12 g (approximately 1 g/cm per side of vulva) of topical anesthetic cream was applied, and the area was covered by plastic wrap 30 min prior to beginning procedure. Alternately, lidocaine was injected (1 mL) every centimeter just prior to the procedure. Episiopeplasty was conducted using standard methods, but employing simple interrupted sutures. Horses were not sedated and use of a twitch was recorded. Four millimeter punch biopsies were harvested 1, 3, and 10 days following episiopeplasty and scored for degree of inflammation by a blinded pathologist. Clinical inflammation scores were assigned when biopsies were obtained. Seven of 11 horses receiving lidocaine infiltration required twitching, but none of the horses that received the anesthetic cream required twitching. Six of 11 and seven of 11 of the lidocaine and anesthetic cream groups, respectively, required twitching for episiopeplasty. Except for the clinical scores on day 3, no statistical differences for clinical and histopathologic scores between samples from the two treatment groups for a given day were identified. Use of lidocaine/prilocaine topical anesthetic cream was as effective as lidocaine infiltration in providing local anesthesia when performing episiopeplasty in mares. Its use decreased the need for twitching horses as well as the risk of deformation of the labia caused by lidocaine infiltration.

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INTRODUCTION

Episiopeplasty is commonly performed on female performance horses, especially race horses, because it is thought that these horses aspirate air into the vulva during exertion and that this may decrease performance. The procedure is also performed on broodmares to minimize aspiration of air into and fecal contamination of the reproductive tract. Local anesthesia during episiopeplasty typically consists of subcutaneous lidocaine infiltration on a line along the mucocutaneous junction of the vulva. After lidocaine infiltration, mares usually show little response to tissue removal and suturing. However, many mares object and require a nose twitch or other forms of restraint during lidocaine infiltration.

EMLA® (Eutectic Mixture of Local Anesthetics) is an eutectic mixture of 5% lidocaine (25 mg/g) and prilocaine (25 mg/g)

that has been used extensively in humans (Buckley & Benfield, 1993). The anesthetic cream was developed as a topical local anesthetic for use in neonates and children, usually for analgesia during intravenous catheterization (Soliman *et al.*, 1988), circumcision (Taddio *et al.*, 1997), vertebral paracentesis (Halperin *et al.*, 1989), and curettage of molluscum contagiosum (Rosdahl *et al.*, 1988). It has also been used successfully for anesthesia of various cutaneous procedures, including split thickness skin graft donor sites (Ohlsén *et al.*, 1985), minor genital surgery (Hallén *et al.*, 1987; Ljunghall & Lillieborg, 1989; Rylander *et al.*, 1990; Cooper, 2002), myringotomy (Whittet *et al.*, 1988), and surgical debridement of leg ulcers in elderly patients (Holm *et al.*, 1990; Malmros *et al.*, 1990; Hansson *et al.*, 1993).

Use of lidocaine/prilocaine anesthetic cream has been studied in animals for venipuncture and skin biopsies (Flecknell *et al.*,

1990; Henfrey *et al.*, 1991; Walzer, 1998). Flecknell *et al.* (1990) concluded that the application of the cream produced good anesthesia in dogs, cats, and rabbits for catheterization. However, it did not appear to produce acceptable anesthesia when applied to the tails of rats. In another study (Henfrey *et al.*, 1991), the cream was considered to provide moderate to good analgesia in the dogs tested compared with lidocaine infiltration for skin biopsies. One dog did not accept application of the cream and blanching of the skin was noted in six of 25 dogs, with loss of surface keratin seen in two dogs. All dogs had skin disease in this study and the use of 1% lidocaine infiltration over anesthetic cream was recommended. The only report of the use of the lidocaine/prilocaine cream in large animals is by Walzer (1998), who found it to be effective for venipuncture and full-thickness skin biopsies when applied to the ears of three white rhinoceroses. To the knowledge of the authors, however, this product has not been studied for use in horses.

Lidocaine/prilocaine topical anesthetic cream has been shown to increase histopathologic evidence of inflammation (Nykanen *et al.*, 1991; Powell *et al.*, 1991). This increased inflammatory response does not hinder wound healing (Nykanen *et al.*, 1991), but it does appear to damage innate tissue defense mechanisms (Powell *et al.*, 1991). This would probably have no effect on healing of sterile wounds, and may, in fact, be beneficial by increasing wound breaking strength, but could be detrimental to the healing of contaminated wounds.

The goal of this study was to compare the local anesthesia and tissue inflammation associated with conventional 2% lidocaine infiltration and 5% lidocaine/prilocaine topical anesthetic cream when used for episioplasty in horses. It was hypothesized that topical application of the anesthetic cream would result in a decreased response from the mare, eliminate the need for additional restraint such as use of a nose twitch, and result in similar or possibly less tissue inflammation than that associated with lidocaine infiltration.

MATERIALS AND METHODS

Test animals

Twenty-two clinically normal mares aged 6.3 ± 4.3 years and weighing 481 ± 51 kg from the Oklahoma State University, College of Veterinary Medicine research herd were used for this study. Mares were housed in $12' \times 12'$ stalls at the Equine Research Park and fed a 14% protein sweet feed (~ 0.5 pound/cwt) divided into two feedings and *ad lib* grass hay. Water and salt blocks were supplied free choice in each stall. Mares were allowed to acclimate to their environment for a minimum of 10 days, after which they received a complete physical examination to confirm the absence of disease.

Episioplasty procedure

Mares were restrained in stocks. All procedures were attempted without use of a twitch. If the mares would not stand

quietly, a twitch was applied to the upper lip and the use of the twitch was recorded. Tails were wrapped and tied to the neck to aid in visualization of the episioplasty site and in maintaining asepsis. The vulva, perineum, and anus were scrubbed with 2% chlorhexidine soap (Nolvasan Surgical Scrub, Fort Dodge Pharmaceuticals, Fort Dodge, IA, USA) and rinsed with water. The vulva was measured and the episioplasty extended from the dorsal commissure ventrally a distance of two-thirds the total length of the vulva. In the lidocaine group, 2% lidocaine HCl (injectable solution; Butler Pharmaceuticals, Columbus, OH, USA; 1 mL/cm of episioplasty site) was injected subcutaneously along the mucocutaneous junction to evert the mucosa using a 20 g, 1.5" needle. For the anesthetic cream group, approximately 1 g/cm per side of vulva of 5% lidocaine/prilocaine topical anesthetic cream (5% EMLA[®] cream, Astra Pharmaceutical Products, Inc., Westborough, MA, USA) was used. The mucous membrane portion of the episioplasty site was dried and half of the dose applied. The remaining cream was applied to the cutaneous area of the episioplasty site and a strip of plastic wrap (Saran Wrap[®] 520 White Plastic Film, Dow Chemical, Midland, MI, USA) was placed over the episioplasty site. The cream and plastic wrap patch were left in place for 30 min prior to beginning the episioplasty. For both groups, an approximately 2–4 mm strip of skin/mucous membrane was removed with surgical scissors along the episioplasty site then sutured with simple interrupted sutures of blue monofilament polypropylene suture (Prolene[®] 0 with a swaged-on cutting FLX needle, Ethicon Inc., Somerville, NJ, USA). Sutures were placed such that three 5–6 mm areas were available between sutures for subsequent biopsy sites.

Biopsy procedure

Punch biopsies (4 mm in diameter) were harvested from the episioplasty site 1, 3, and 10 days following the procedure. Prior to each biopsy procedure, a clinical inflammation score from 0 to 4 was assigned with 0 = no swelling or scaling, 1 = mild scaling with no obvious swelling, 2 = mild swelling \pm moderate scaling, 3 = moderate swelling \pm moderate scaling, 4 = severe swelling and/or severely reddened, bleeding, or excoriated. Biopsy specimens were placed in 10% formalin and labeled as to date and horse number. Specimens were bisected, processed in a graded series of alcohol, embedded in paraffin, sectioned at 4–5 microns, and stained with hematoxylin and eosin. Following histologic examination, specimens (two sections) were given a histologic inflammation score with 1 = minimal edema and no cellular infiltrate, 2 = mild edema (epidermal \pm dermal) and mild, primarily neutrophilic cellular infiltrate, 3 = moderate edema (epidermal \pm dermal) and/or moderate neutrophilic or mixed neutrophilic and mononuclear infiltrate, and 4 = severe edema \pm severe inflammatory cellular infiltration. Additional comparisons were made based on pattern of inflammatory infiltration (diffuse, nodular, perivascular, etc.) and the degree, if any, of granulation tissue or fibrosis, or epithelial changes present.

Study design

Mares were paired by age and weight and divided into two groups of 11 such that each group was approximately the same mean age and weight. Groups were then randomly assigned to receive topical anesthesia or lidocaine infiltration. One surgeon (CGM) performed all episioplasty procedures. Biopsy specimens were evaluated and scored by a pathologist (GC) who was masked as to the treatment group of the samples.

Statistical analysis

All analyses were performed with PC SAS Version 8.2 (SAS Institute, Cary, NC, USA). The need to use a twitch to restrain animals for anesthesia and surgery was evaluated using a Fisher's Exact Test with two-sided probability (PROC FREQ in SAS). The effect of anesthetic treatment on external signs of inflammation and tissue reaction was evaluated by defining response grades for each criterion. Data from each biopsy period were analyzed using an analysis of variance with repeated measures (PROC MIXED in SAS). The results were considered significant for $P < 0.05$.

Animal welfare

In conducting this study, the investigators complied with all Federal, State, local and institutional laws and guidelines pertaining to the care and treatment of laboratory animals following the USDA guidelines for equine research. This study was approved by the Oklahoma State University Institutional Animal Care and Use Committee.

RESULTS

Approximately 20 min after application of the anesthetic cream, mild (1), mild to moderate (1), and moderate (2) tissue swelling was noted in four mares, with reddening of the haired skin noted in one mare in addition to the swelling. No swelling or inflammation was noted for mares in the lidocaine group aside from the temporary deformation caused by the lidocaine infiltration. One mare in the anesthetic cream treatment group objected to all procedures near the vulva, including scrubbing and cream application.

Twitching

Seven of 11 mares required twitching during lidocaine infiltration. This was a significantly higher ratio than in the anesthetic cream group, none of which required the application of a twitch. During the episioplasty, however, there was no significant difference between the two treatment groups regarding the number of mares that required twitching (six of 11 for the lidocaine group, seven of 11 for the anesthetic cream group), thus indicating similar degrees of anesthesia.

Table 1. Mean scores and standard errors (SEs) for clinical inflammation at the time of biopsy 1, 3, and 10 days following an episioplasty procedure in 11 mares

Treatment group	Mean clinical scores		
	Day 1	Day 3	Day 10
2% Lidocaine	1.64 ^a	1.00 ^a	0.36 ^a
SE	0.15	0.27	0.15
5% Lidocaine/prilocaine	1.82 ^a	1.73 ^b	0.73 ^a
SE	0.12	0.30	0.14

Clinical inflammation was scored from 0 to 4 with 0 = no swelling or scaling, 1 = mild scaling with no obvious swelling, 2 = mild swelling \pm moderate scaling, 3 = moderate swelling \pm moderate scaling, 4 = severe swelling and/or severely reddened, bleeding, or excoriated. At any given time period, mean values with the same superscript letter are not significantly ($\alpha = 0.05$) different as determined by use of a least significant difference procedure.

Clinical inflammation score

A significant difference in the average clinical score between treatment groups was noted on day 3 with the lidocaine infiltration group showing less inflammation than the topical anesthetic group. However, there was no significant difference in clinical score between treatment groups when biopsies were obtained at 1 and 10 days following the procedure (Table 1). The average score decreased at each time period observed. No epithelial sloughing or redness was noted from mares in the lidocaine treatment group. Within the anesthetic cream group, superficial epithelial sloughing and redness was observed on day 1 (two mares) and day 3 (three mares). No mare had signs of sloughing at both time periods.

Histopathology

Improvement in histopathologic parameters occurred with each successive biopsy for both treatment groups (Table 2). While there was a trend toward increased inflammation with the anesthetic cream treatment group at day 1, there were no statistical differences in scores for any of the histopathology criteria at any time period.

DISCUSSION

The results of this study indicate that under the experimental conditions tested, use of 5% lidocaine/prilocaine topical cream was as effective as 2% lidocaine infiltration for anesthesia when performing episioplasty procedures on mares. The inflammation at the episioplasty site was not significantly increased with application of the topical cream compared with lidocaine infiltration. Therefore, 5% lidocaine/prilocaine topical anesthetic cream can be used as an effective and safe alternative anesthetic product when performing episioplasty procedures in horses.

The use of a twitch for restraint of a horse is controversial. Many horse owners will not allow clinicians to apply a twitch to

Table 2. Mean scores and standard errors (SEs) for clinical inflammation and histopathologic parameters from biopsy samples obtained 1, 3, and 10 days following an epispioplasty procedure in 11 mares

Treatment group	Mean histopathology scores											
	Overall severity			Inflammation			Spongiosis			Edema		
	Day 1	Day 3	Day 10	Day 1	Day 3	Day 10	Day 1	Day 3	Day 10	Day 1	Day 3	Day 10
2% Lidocaine	3.27	2.36	2.00	2.09	1.91	1.64	2.91	1.82	1.45	1.82	1.82	1.36
SE	0.30	0.20	0.27	0.31	0.16	0.31	0.31	0.26	0.21	0.26	0.23	0.15
5% Lidocaine/prilocaine	3.73	2.64	1.73	2.73	2.36	1.64	2.91	1.55	1.09	1.91	1.91	1.55
SE	0.20	0.31	0.20	0.30	0.31	0.20	0.31	0.21	0.09	0.16	0.28	0.16

Specimens were given a histologic inflammation score with 1 = minimal edema and no cellular infiltrate, 2 = mild edema (epidermal \pm dermal) and mild, primarily neutrophilic cellular infiltrate, 3 = moderate edema (epidermal \pm dermal) and/or moderate neutrophilic or mixed neutrophilic and mononuclear infiltrate, and 4 = severe edema \pm severe inflammatory cellular infiltration. No significant differences ($\alpha = 0.05$) were found between treatment groups for any histopathology scores at any given time period.

their animals, because they consider this practice to be an inhumane form of restraint. When performing an epispioplasty, a twitch is often needed when anesthetizing the skin, even in sedated horses. In our study, seven mares required twitching during lidocaine infiltration of the vulvar labia, whereas none required twitching with application of anesthetic cream. Twitching during epispioplasty was required in six and seven horses in the lidocaine and anesthetic cream treatment groups respectively. One mare in the anesthetic cream group, however, objected to all procedures being performed near the vulva, including scrubbing. It should be noted that none of the mares in this study were sedated at any time during the epispioplasty procedure. Sedation during epispioplasty may eliminate the need for a twitch in many cases.

Mild to moderate swelling was noted approximately 20 min after application of the cream in four horses, with one horse also showing some mild reddening. It was impossible to identify swelling in the lidocaine group because of distortion of the labia caused by the infiltrate; however, no inflammation was noted prior to beginning the epispioplasty. In humans, side effects are uncommon, but are usually mild, and may include edema, burning sensation, transient paleness, and erythema (Lycka, 1992). No side-effects were noted in rhinoceroses (Walzer, 1998). However, Henfrey *et al.* (1991) reported blanching of the skin in 25% of the dogs. Similar to our study, one dog would not tolerate application of the anesthetic cream. It is unknown whether the cream caused transient irritation or if the reaction of these individuals was behavioral in origin.

Application of 5% lidocaine/prilocaine topical anesthetic cream under occlusion to the labia of mares for 30 min was as effective as lidocaine infiltration for providing anesthesia for the epispioplasty procedure. In humans, the cream has been shown to have an observable effect 30–60 min after application, but produced the most reliable anesthesia after 90–120 min when applied to the human forearm (Lycka, 1992). EMLA[®] patches applied to the ears of rhinoceroses for 60–90 min produced good analgesia allowing venipuncture and skin biopsies (Walzer, 1998). A human racial difference in effectiveness was noted with Black patients achieving a lower

level of anesthesia compared with White patients. Presumably, this is because of differences in the rates or extents of anesthetic penetration due to the density of the stratum corneum or binding to skin pigments (Lycka, 1992). Thickness and condition of skin are also important when determining the duration of application. Juhlin *et al.* (1989) found that maximum plasma concentrations of the drugs occurred rapidly and were higher when the cream was applied to facial skin as opposed to skin of the forearm. Additionally, the drugs were absorbed more rapidly across diseased skin, with anesthesia achieved in 15 min vs. 60 min for normal skin in a comparable location. When applied to the genital mucosa of women, satisfactory anesthesia occurred in 90% of the patients within 5–10 min (Ljunghall & Lillieborg, 1989). Although not statistically significant, there was a trend toward decreased analgesic efficacy with application times greater than 15 min. A similar time to onset of anesthesia was noted by Rylander *et al.* (1990). In the treatment of genital warts, Rylander *et al.* (1990) and Hallén *et al.* (1987) reported adequate anesthesia in men with application times of 3–35 min, whereas adequate anesthesia in women tended to require longer times (median 50 min). When applied to the gingival mucosa in humans for 3, 5, and 10 min, there was significant reduction of the pain threshold at all application times, but no significant differences between the application times (Barcohana *et al.*, 2003). In our study, we found no significant difference between treatment groups in the need to twitch mares during the epispioplasty procedure. This would indicate that application of the 5% lidocaine/prilocaine cream for 30 min is at least as effective for performing an epispioplasty as is 2% lidocaine infiltration. However, the time to onset of maximal anesthesia for the anesthetic cream group was not established. It may be that a longer or shorter application time is required for full anesthetic benefits.

When skin biopsies were obtained from epispioplasty sites for histopathologic examination, the sites were evaluated for clinical inflammation based on skirting, edema, reddening, bleeding and excoriation. While several mares in the anesthetic cream group had superficial epithelial sloughing, a statistical difference between the two groups with regard to

clinical signs of inflammation was noted only on day 3 following the episiotomy. By day 10, however, there was no difference in clinical scores between the two groups. In a study comparing EMLA[®] to 1% lidocaine infiltration on wound healing in rats, there was a trend toward increased inflammation in the EMLA[®] group (Nykanen *et al.*, 1991). As with our study, this was not statistically significant and there were no adverse effects on healing noted. The longer duration of observable inflammation is likely to be unimportant clinically, especially given the histopathological results. However, this may not hold true with contaminated wounds in which the use of lidocaine/prilocaine cream significantly damaged tissue defense mechanisms (Powell *et al.*, 1991). Suppression of defense mechanisms may only have clinical significance in cases where contaminated wounds are to be sutured for healing by primary intention. For chronic wounds or large wounds that will heal by second intention, EMLA[®] cream has been shown to provide excellent anesthesia for wound debridement (Malmros *et al.*, 1990; Hansson *et al.*, 1993; Blanke & von Hallern, 2003) and may actually be beneficial for the healing of sterile surgical wounds, as topical anesthetics have been shown to have antimicrobial activity (Schmidt & Rosenkranz, 1970; Wimberley *et al.*, 1979).

Lidocaine/prilocaine topical cream has several advantages over the traditional lidocaine infiltration for episiotomies. The cream was applied topically and was well tolerated by most of the mares with no need for twitch application as opposed to traditional anesthetic. Although a small degree of edema and inflammation occurred in a few mares in the anesthetic cream group, there was no substantial deformation of the labia. Additionally, use of sedation may eliminate the need to twitch mares during the episiotomy procedure. The major disadvantage of the anesthetic cream as compared with lidocaine is the time to onset of anesthesia, as lidocaine infiltration allows the clinician to start the procedure almost immediately. While inflammation may be slightly increased with the use of the topical anesthetics, it has been shown to produce an increased wound-breaking strength (Powell *et al.*, 1991), likely due to the exaggerated inflammatory response.

This study has shown that 5% lidocaine/prilocaine topical anesthetic cream is as effective as 2% lidocaine infiltration for anesthesia of the vulvar labia of mares when performing an episiotomy. It decreases the need for twitching, which may be of concern for some clients. Additionally, the anesthetic cream may have applications for use in veterinary medicine that require only topical anesthesia and which are performed under aseptic techniques. Use on contaminated wounds may be contraindicated as anesthetic cream has been shown to reduce tissue defense mechanisms; however, it has been successfully used for years in the debridement of wounds. Caution is indicated when using this product, especially in neonates or small animals, because of reported hematological and central nervous system toxicity. Further studies are required to determine time to onset of maximal anesthesia as well as its use in other procedures, such as skin biopsies, wound debridement, and i.v. catheterization.

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