RESEARCH PAPER

Effect of preemptive topical application of lidocaine or prilocaine–lidocaine on successful catheterization of ear veins in New Zealand White rabbits

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Abstract

Objective To compare 5% lidocaine ointment applied for 10 minutes before intravenous (IV) catheterization to a eutectic mixture of local anesthetics (2.5% lidocaine and 2.5% prilocaine; EMLA) cream applied for 10 or 60 minutes prior and a water-based placebo for 60 minutes for successful marginal ear IV catheterization in rabbits.

Study design Randomized, blinded, complete crossover, controlled trial.

Animals A total of 10 intact male, New Zealand White rabbits aged 4 months.

Methods After application of one of the treatments on the marginal ear vein, an operator unaware of the treatment attempted IV catheter placement. Successful IV catheterization was considered as a catheter inserted at the first attempt, safely secured, with appropriate patency. Generalized linear mixed models were developed to identify relevant predictors of successful catheter placement.

Results Ears that had EMLA cream applied 60 minutes before the catheterization attempt had more than 10 times the odds of successful catheter placement [odds ratio (OR)= 10.75; 95% confidence interval (CI), 1.92–60.16; $p < 0.008$] compared with placebo. Both the application of EMLA cream or lidocaine ointment 10 minutes before the catheterization attempt resulted in approximately three times the odds of successful catheter placement compared with placebo, but were not statistically significant.

Conclusions and clinical relevance Application of EMLA cream on the marginal ear vein 60 minutes before catheterization increases the chance of successful IV catheter placement in conscious rabbits.

Keywords catheterization, intravenous catheter, lidocaine, lidocaine/prilocaine, marginal ear vein.

Introduction

Rabbits are the third most common animal found in animal rescues in the USA and the third most popular pet in the UK (DeMello 2016). With the growing popularity of rabbits as pets and the increasing standard of care that owners expect, the need to reduce pain and stress to facilitate clinical procedures is important. As prey species, rabbits are prone to stress and methods to minimize stress may reduce the chance of injury and morbidity (Lloyd 2017). Veterinary procedures such as advanced imaging, dental care and sterilization surgery may be indicated for rabbits, and placing an intravenous (IV) catheter may be part of these procedures for drug administration. IV access also facilitates fluid and vasoactive therapy and perioperative analgesia, which may contribute to decreasing the high anesthesia morbidity and mortality risk in rabbits (Brodbelt et al. 2008).

Insertion of an IV catheter can be difficult in rabbits with small ears or when the operator lacks experience in the procedure. Handling and restraint and pain or discomfort during catheterization may induce stress in the rabbit. Application of

local anesthetics to the site of catheterization may minimize stress and pain. Lidocaine-containing topical products are available in various formulations (Carney et al. 2012; Benato et al. 2019; Chávez et al. 2021; Leask 2021). A eutectic mixture of 2.5% lidocaine and 2.5% prilocaine (EMLA cream) has been used topically in many veterinary species and in human medicine to enable percutaneous catheterization or venipuncture without pain or discomfort (Walzer 1998; van Oostrom & Knowles 2018; Crisi et al. 2021; Leask 2021). Keating et al. (2012) found that EMLA cream prevented signs of pain in rabbits during ear tattooing procedures after being applied to both sides of the ears for 20 minutes when compared with animals without treatment. Untreated rabbits struggled and vocalized more and had higher scores for the pain grimace scale. In one study, EMLA cream facilitated catheterization in rabbit marginal ear veins even 60 minutes after topical application (Flecknell et al. 1990). However, a delay of 60 minutes may not be practical and a shorter time may be more clinically useful.

Although EMLA cream is effective for topical anesthesia in rabbits and other species (Longley 2008; Söbbeler & Kästner 2018; van Oostrom & Knowles 2018; Benato et al. 2019; Leask 2021), there is less information about lidocaine-containing topical products. Lidocaine ointment is an over-the-counter, widely available and inexpensive product commonly used as a topical anesthetic in human medicine, with an effect comparable with that of EMLA cream (Herberger et al. 2012). In veterinary medicine, lidocaine has historically been used as an injectable local anesthetic or topical patch. A study determined that 5% lidocaine cream decreased the pain of injections for intradermal allergy testing in dogs compared with a lidocaine patch or placebo (Tomich et al. 2021). Further study of topical lidocaine cream *versus* EMLA cream in rabbits is indicated.

This study sought to compare the success of venous catheterization in rabbits after topical application of EMLA or lidocaine ointment. The effect of duration of contact of EMLA cream for 60 minutes (Flecknell et al. 1990) was compared with 10 minutes to investigate a more practical technique for clinical practice. Our hypotheses were 1) that lidocaine ointment applied 10 minutes before IV catheterization would be comparable to EMLA cream applied for 60 minutes on success of IV catheterization in rabbits; and 2) that EMLA cream applied 10 minutes before IV catheterization would be comparable to EMLA cream applied for 60 minutes on success of IV catheterization.

Materials and methods

Animals

A total of 10 intact male, New Zealand White rabbits, aged 4 months and weighing 2.49−3.04 kg, were used for this study. The rabbits originated from a commercial vendor (Charles River Laboratories, MA, USA) and were microchipped for identification. The animals were deemed healthy based on physical examinations. The animals were housed individually in metal cages at the Oklahoma State University Animal Resources facility. Each rabbit had two water bottles with tap water, one pelleted food container and one plastic enrichment toy. The rabbits were fed a standard laboratory rabbit pelleted diet (5321; LabDiet, MO, USA). Animals were kept on 12 hours light and 12 hours dark circadian rhythm at a room temperature of 19.4 °C with a 30−70% humidity range. Before any procedure, the study was approved by the Oklahoma State University Institutional Animal Care and Use Committee (no. 21-11) and follows animal ethical guidelines and national laws. The rabbits and operators had a week of practice prior to the study for acclimatizing to restraint and handling, but no IV catheterization was performed in these animals. The rabbits were used for a concurrent study investigating body temperature measurement (data not shown). All animals were adopted following the experiments.

Study design and outcomes

This study was a blinded, complete crossover, controlled trial. The primary outcome of the study was successful catheter placement. Randomization of treatment schedule and ear assigned to each operator were determined by online software (randomizer.org). The operator placing the catheter was unaware of the treatment applied to the ear.

Study procedures

The study was carried out in four rounds and all 10 rabbits were investigated in each round. Each round was divided into two blocks conducted over the course of 4 days, for a total of 16 calendar days. Each block of the experiment was followed by at least 3 days of wash-out period. The completion of block 2 of the experiment was followed by 3 days of wash-out period. Time restraints allowed five rabbits to be investigated each day. On block 1, day 1, one operator applied the treatments and restrained five animals, while the other operator placed the catheters. On block 1, day 2, the remaining five rabbits had one ear catheterized with the operators having the same roles as on day 1. The next day, which was block 2, day 1, the role of the operators was reversed and the ear that was not previously catheterized in block 1 was used. On block 2, day 2, the remaining five ears were catheterized by the same operator as for block 2, day 1. Three days of a wash-out period then began the next day. This schedule was repeated for a total of four rounds.

During the study, two operators (SJ and DL) placed the catheters. Both were veterinary students who had no previous experience placing catheters and were specifically trained on

catheter placement on sedated rabbits (rabbits from a different protocol, data not shown) prior to starting the investigation. Throughout the study, each ear was used four times, each treatment was applied 20 times and each operator attempted to place 40 catheters. A total of 80 catheterization placement events were performed. The treatment creams were prepared by a third operator (JB) and placed in opaque jars labeled with letters, to ensure blinding of both operators. The order of treatment applied and rabbit ear for each operator was determined using an online randomizer software (www.randomizer.org).

Catheter placement

The fur on the randomly selected ear was clipped (7.5−10 × 2.5 cm) on the first day with a #40 blade on standard clippers. Clipping was necessary to observe the injection of saline and was generally performed twice weekly. The randomly assigned treatment was applied to the ear for the predetermined amount of time (10 or 60 minutes). Treatments included EMLA cream (prilocaine 2.5% and lidocaine 2.5% USP; Tolmar Inc., CO, USA) applied for 60 or 10 minutes (treatments EMLA-60 and EMLA-10), lidocaine ointment (Lidocaine ointment USP, 5%; Glenmark Pharmaceuticals Ltd, India; treatment LIDO-10) for 10 minutes, or a water-based lubricant placebo (Surgilube; HR Pharmaceuticals Inc., PA, USA; treatment placebo) for 60 minutes. The randomly selected animal was restrained by only the operator who was scheduled for restraining that day, and treatment was applied. Only the operator applying the treatment was present in the room and the application timing was performed in a way that the operator placing the catheter was unaware of it. A 1 mL syringe was filled with the treatment and then applied to the ear with a gloved hand. No occlusive dressing was applied over the area. The rabbit was then returned to the cage and monitored to prevent scratching of the ear. After the predetermined application period (10 or 60 minutes), the rabbit was physically restrained again by the same operator and any excess treatment was cleaned with gauze to maintain blinding for the person placing the catheter. Restraint involved placing the rabbit on a towel spread open on a table. Then the towel was wrapped around the rabbit so that the head and ears were exposed, but the rest of the body was secured within the towel. The restraining operator then placed one hand at the base of the neck with their body serving as a barrier on one side and their forearm on the other side of the rabbit. This allowed the other hand to be used to occlude the vein by applying pressure at the base of the ear. The external surface of the pinna was aseptically prepared for catheterization using 4% chlorhexidine solution followed by 75% alcohol. A 24 gauge, 19 mm catheter (Becton Dickinson Infusion Therapy Systems Inc., UT, USA) was placed in the marginal ear vein by the other operator. Only one attempt was allowed. Once the catheter was placed, it was capped with an injection port and a foam block was placed on the inner surface of the pinna to support the ear and catheter. Adhesive tape (Blue-Point Laboratories, PA, USA) was then used to secure the catheter by wrapping it around the catheter and ear. This was followed by a self-adherent bandage (Cohesiant Wrap; Blue-Point Laboratories). The catheter was flushed with 1−3 mL of 0.9% saline to check for patency. Successful catheter placement was defined as a catheter inserted in the vein at the first attempt, safely secured and patent and allowing free flow of saline. If any of the latter was not possible, the catheterization event was considered a failure. If there was a response such as resisting restraint or head shaking before the catheter penetrated the skin, then the attempt was continued. However, if the catheter penetrated the skin and the animal jumped or shook its head causing the catheter to fall out, then the attempt was considered a failure. If the catheter had pierced the skin and the animal's reaction did not cause the catheter to fall out, then the attempt was continued. Once the catheter success was determined, all equipment was removed, digital pressure was applied as needed, and the rabbit was returned to the cage. The ears were monitored during the study period every other day for hyperemia, bruising or crusting. For the 4 months after the conclusion of the study, the ears were monitored weekly for evidence of inflammation or necrosis.

Statistical analysis

Categorical variables were reported as percentages of rabbits in each category. Generalized linear mixed models (GLMM) with a binary outcome (success/failure) were developed to identify any relevant predictor of successful catheter placement, accounting for an individual rabbit as a random effect. Fixed effects tested were the order of the procedure (from 1 to 8, included in two different models as categorical and as an ordinal variable), operator, ear catheterized (right/left) and treatment administered. Odds ratios (OR) and 95% confidence intervals (CI) were initially calculated through univariable GLMM that included the individual rabbit as a random effect. The adjusted odds ratios (aOR) were calculated through a multivariable GLMM that included operator, order of the procedure (ordinal) and treatment administration, in addition of rabbit as a random effect. Multivariable GLMMs were subsequently developed to evaluate whether the association between treatment administered and successful IV catheter placement persisted after adjustment for prespecified potential confounders [operator, order of the procedure (ordinal)] regardless of their statistical significance in the univariable analysis. aOR and 95% CI were reported to quantify the strength of these associations. Data were analyzed using SPSS Statistics, Version 26.0 (IBM Corp., IL, USA). Two-tailed values of $p < 0.05$ were considered significant.

Results

A total of 80 catheterization attempts were performed on a total of 16 calendar days. Overall, success rate in treatment EMLA-60 was 55% (11/20 attempts) (Table 1). Fewer attempts were successful in treatments LIDO-10 and EMLA-10 at 30% (6/20 attempts) and 25% (5/20 attempts), respectively. Successful catheterization was 10% (2/20 attempts) in treatment placebo. No morbidity or mortality was detected during the study. In addition, no clinically relevant abnormality was detected on either ear through the study period or during the following 4 months.

In the unadjusted analyses, treatment EMLA-60 resulted in a 10-fold increase in OR for successful catheter placement (OR=10.75; 95% CI, 1.92−60.16; $p < 0.008$) when compared with placebo treatment. Treatments EMLA-10 and LID-10 did not result in a statistically significant higher proportion of successfully placed catheters than the placebo treatment (Table 1). Other predictors tested (operator, ear and overall attempt number) were not associated with successful IV catheter placement. After multivariable adjustment, the association between treatment and successful placement persisted, with odds of successful IV placement approximately 12-fold when EMLA cream was applied 60 minutes before the attempt (aOR=11.86; 95% CI, 2.02−69.47, $p = 0.007$). The odds of successful placement with other treatments or considering other variables were not different (Table 1).

Discussion

The results of this study indicate that applying topical EMLA cream on the marginal ear vein 60 minutes before attempting to place an IV catheter results in a higher chance of success than a placebo. Application of either EMLA cream or lidocaine ointment for a shorter duration (10 minutes) resulted in a nonstatistically significant increase in the success of placing an IV catheter. This study supports previous publications that showed a benefit to using local anesthetics in rabbits prior to other procedures of the ear (marginal ear vein venipuncture and ear tattooing) (Flecknell et al. 1990; Keating et al. 2012). These results may have a relevant impact in clinical rabbit medicine, where diseased rabbits often need vascular access and avoiding chemical restraint for catheter placement could be beneficial, and in laboratory animal medicine to reduce the stress of rabbits undergoing this procedure without administering parenteral medications.

Application of EMLA cream 10 minutes before attempting marginal ear IV catheterization was not found to be as effective as applying EMLA cream 60 minutes before attempting IV catheterization. The shorter application resulted in approximately three-fold odds of successful catheter placement when compared with the placebo, but the results were not statistically significant. The manufacturer's instructions recommend that the product be applied at least an hour before any procedure in people. Some veterinary studies support this as they found that

Table 1 Results of attempted placement of a catheter in a marginal ear vein of 10 rabbits after topical application of one of four treatments: treatment placebo, water-soluble gel for 60 minutes; treatment LIDO-10, lidocaine ointment 5% for 10 minutes; EMLA-10, prilocaine−lidocaine cream for 10 minutes; EMLA-60, prilocaine−lidocaine cream for 60 minutes. CI, confidence interval.

Variable	Category	Success, *n* (%)	Failure, *n* (%)	Odds ratio	95% CI	*p*	Adjusted odds ratio	Adjusted 95% CI	Adjusted *p*
Operator	1	9 (22.5)	31 (77.5)	Ref	–	–	Ref	–	–
	2	15 (37.5)	25 (62.5)	2.06	0.76−5.58	0.151	2.42	0.79−7.44	0.122
Ear	Left	11 (27.5)	29 (72.5)	Ref	–	–			
	Right	13 (32.5)	27 (67.5)	1.27	0.48−3.36	0.628			
Attempt number	1	3 (30)	7 (70)	Ref	–	–			
	2	3 (30)	7 (70)	1	0.14−6.99	1			
	3	3 (30)	7 (70)	1	0.14−6.99	1			
	4	2 (20)	8 (80)	0.58	0.07−4.71	0.608			
	5	3 (30)	7 (70)	1	0.14−6.99	1			
	6	5 (50)	5 (50)	2.33	0.36−15.02	0.37			
	7	0 (0)	10 (100)	0.7	0.00−3.82	0.188			
	8	5 (50)	5 (50)	2.33	0.36−15.02	0.37			
	Ordinal			1.03	0.84−1.28	0.751	0.96	0.75−1.23	0.744
Treatment	Placebo	2 (10)	18 (90)	Ref	–	–	Ref	–	–
	LIDO-10	6 (30)	14 (70)	3.78	0.65−22.05	0.137	4.11	0.66−25.50	0.127
	EMLA-10	5 (25)	15 (75)	2.94	0.489−17.71	0.235	3.04	0.49−18.72	0.227
	EMLA-60	11 (55)	9 (45)	10.75	1.92−60.16	0.008	11.86	2.02−69.47	0.007*

*Significantly different from placebo treatment ($p < 0.05$).

EMLA cream was successful when applied 60 minutes prior (Flecknell et al. 1990; Walzer 1998; van Oostrom & Knowles 2018). Nevertheless, other studies have found that a reduced time of 30 minutes of application time was comparable in dogs, cats, or even at 20 minutes with sedated cats (van Oostrom & Knowles 2018; Oliveira et al. 2019; Crisi et al. 2021). The differences in the efficacy of EMLA cream application can be attributable to inherent species differences in skin, degree of drug absorption, the surface area of the body and duration of contact time (Keating et al. 2012). EMLA cream has also been shown to have an initial vasoconstrictive effect followed 2−3 hours later by vasodilation in humans (Ashley et. al 1999). As of this study, no studies have been published in rabbits to assess the degree of transdermal absorption or vasoactive effects of lidocaine or lidocaine−prilocaine combinations regarding these factors. The increasing odds of successfully placing an IV catheter observed in the present study suggest that a prolonged contact time does increase the efficacy of EMLA cream in rabbits.

Lidocaine ointment applied for 10 minutes before IV catheterization was not statistically different from the placebo application in successful IV catheter placement. However, the odds of success were three and four times greater than the placebo in the unadjusted and adjusted analysis, respectively. This may have also been influenced by species differences as discussed for EMLA cream or a lower efficacy of the topical lidocaine ointment preparation used in this study (Söbbeler & Kästner 2018). However, when intradermal injections were administered in dogs, it was found that 5% lidocaine cream provided the most significant reduction in pain scores compared with a 5% lidocaine patch or a control without active ingredients (Tomich et al. 2021). In human medicine, topical lidocaine formulations had no significantly different effects from EMLA cream in efficacy of local anesthesia with standardized prick pain (Herberger et al. 2012). Results from the present study suggest that the classic formulation of lidocaine ointment provides analgesia and if applied for 60 minutes may have had the same effect as EMLA cream. Further research will need to be pursued regarding use of topical lidocaine in rabbits.

Limitations of the present study include the lack of experience of the operators (veterinary students with no previous experience in placing IV catheters). However, both operators were specifically trained in this procedure prior to the study. These individuals practiced placing catheters under the supervision of an experienced clinician (JB) on sedated rabbits (eight for each student) from a different study. The results of the present study may have been different if veterinarians or technicians with experience in catheter placement in rabbits were involved. Nonetheless, no statistical difference was found between the two operators, and similarity in experience may have decreased variability. The results support a benefit of local anesthetic cream for modifying rabbit behavior when inexperienced personnel may require more than one attempt at venipuncture or catheterization (Flecknell et al. 1990; Keating et al. 2012; van Oostrom & Knowles 2018; Leask 2021). The use of EMLA cream can improve animal welfare especially during training of veterinary and laboratory techniques.

An occlusive bandage was not used following the application of the EMLA cream or lidocaine ointment in this study. The bandage is suggested by the manufacturers to increase transdermal absorption of the products. Occlusal dressings have also been used in veterinary medicine to prevent the animal licking the product. A disadvantage is that the dressing can be stimulating to the rabbits. Therefore, not using an occlusal dressing may have decreased the amount of drug absorbed and reduced efficacy. By contrast, several veterinary studies and anecdotal experiences report local anesthetic effects in the absence of an occlusal dressing (Söbbeler & Kästner 2018; Oliveira et al. 2019). In the present study, the animals were monitored to prevent them from scratching their ears and removing the products by grooming.

A confounding variable to the present study was stress. Stress can contribute to vasoconstriction and behavioral responses that make catheter placement difficult (Greaney et al. 2020). An assessment of the rabbit compliance, stress or pain was not included in the study design to record differences between treatments and treatment times. These assessments could have confirmed a higher success rate with the longer contact time. The rabbits in treatment EMLA-60 may have had fewer adverse reactions to the needle prick because the longer contact time resulted in improved local analgesia or because the longer time between handling minimized the stress response. Catheterization may have been more difficult in treatments EMLA-10 and LIDO-10 because handling after only 10 minutes may have resulted in greater resistance to restraint and stress, in turn leading to vasoconstriction and more difficult catheter insertion. Future studies on the effect of local anesthetics would benefit from assessing compliance in veterinary patients to further understand their use and effects.

Conclusions

The topical application of EMLA cream to the skin over an auricular vein for 60 minutes before attempting IV catheterization in rabbits was the most effective method for successful outcome in this study. Lidocaine ointment or EMLA cream applied for 10 minutes resulted in more successful attempts in IV catheterization than after application of a placebo. Application of EMLA cream for 60 minutes prior to IV catheterization facilitated successful catheter placement in New Zealand White rabbits by inexperienced operators.

Acknowledgements

Funding for this project was provided by the Oklahoma State University Department of Veterinary Clinical Sciences, the Summer Research Training Program and the Dr. Kristie Plunkett Exotic Animal Fund.

Authors' contributions

GHC: data interpretation, preparation of manuscript. NDG: statistical analysis, preparation of manuscript. SJ and DL: study design, data collection, preparation of manuscript. LC: data management, preparation of manuscript. JB: study design, data collection, data management, preparation of manuscript. All authors read and approved the final version of this manuscript.

Conflict of interest statement

The authors declare no conflict of interest.

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Received 26 February 2022; accepted 23 June 2022.

Available online 30 June 2022

