Grant Expenditure Responsibility Reports

2010
USEF Equine Health Research Fund

$24,971

For Research by Michigan State University into whether Lidocaine Improves Recovery of the Equine Large Colon After Ischemic Injury

The Effect of Lidocaine on Recovery of Injured Equine Large Colon

Introduction:

One of the most severe forms of colic is a twisted colon. The twist blocks the blood flow to the colon and causes the cells that line the intestine to die. Even with immediate surgery, loss of these cells allows toxins that are in the horse's gut to cross into the circulation and cause severe problems such as founder, kidney failure and death. This problem is extremely important in performance and show horses that are at a high risk for colic because of their high grain diet. This is emotionally and financially stressful for owners, as horses with a twisted colon do not survive as often as horses with other types of colic and the treatment is very expensive.

Lidocaine is a local anesthetic commonly used for nerve blocks but it also has anti-inflammatory effects which could improve the repair of the intestinal lining. We previously discovered that lidocaine improves healing of damaged small intestine. In this study we evaluated the effect of lidocaine in damaged large colon.

Our ultimate goal was to see if lidocaine improved the repair of the lining of the intestine so that fewer toxins are absorbed and horses have a better chance of surviving after surgery.

Methods:

To do this, we used 12 unwanted donated horses with no history of colic. Six horses were treated with intravenous lidocaine and 6 were given normal intravenous fluids (LRS) with horses randomly assigned to each group. We blocked the blood supply to part of the colon that included the right dorsal colon and the pelvic flexure for 2 hours while the horses were under anesthesia, and then allowed the blood to return and the intestine to recover for 18 hours before the horses were euthanized. The assigned treatment was started immediately after the horse was anesthetized and was continued until euthanasia. All horses were carefully monitored by checking their vital signs and behavioral pain scores before surgery and at 4, 8 and 18 hours after the end of surgery. After euthanasia we collected the lining of the intestine from the damaged colon and adjacent undamaged colon. We evaluated the lining of the intestine in Ussing chambers to see how resistant it was to electrical current and to toxins passing through it. We also collected blood samples from the horses before surgery (baseline) and 8 hours after the end of surgery to measure the levels of inflammatory products which make the horse sick and painful after surgery. Statistical analyses were performed on the results with significance set at $P<0.05$.

Results:

Behavioral pain scores were significantly higher after surgery in both treatment groups but were not significantly different between treatment groups at any time. Heart rate was also significantly increased after surgery in both treatment groups but it was significantly lower in the lidocaine treated horses than the LRS treated horses 4 hours after the end of surgery (LRS mean 52 beats per minute compared to lidocaine mean 42 beats per minute). Electrical resistance was significantly higher in the damaged right dorsal colon from horses treated with lidocaine compared to horses treated with LRS. However, there was no difference found in the electrical resistance between treatment groups in the damaged pelvic flexure. As expected, more toxin leaked across the damaged colon than across undamaged colon. However in the right dorsal colon this increase was significantly less in the colon from horses treated with lidocaine. No such effect of

treatment was found in the pelvic flexure. The concentration of the inflammatory product thromboxane was significantly increased after surgery in horses treated with lidocaine and was significantly higher than the concentration in LRS treated horses. There was no effect of surgery or treatment on the concentration of the inflammatory product prostaglandin E_2.

Discussion:

Lidocaine improved the recovery of the lining of the damaged right dorsal colon. This was shown by an increase in electrical resistance and reduced leakage of toxin across the lining. Interestingly no effect of lidocaine treatment was found in the pelvic flexure region of the colon. This may be because the pelvic flexure is more resistant to loss of blood supply than the right dorsal colon and therefore the injury was not severe enough to detect an effect of treatment at this site. Lidocaine had no effect on behavioral pain scores confirming that it does not provide pain relief when used in this way, which corroborates the findings of other studies. Lidocaine had little effect on the horses' vital signs except for a transiently lower heart rate 4 hours after surgery.

Conclusion:

Overall, lidocaine improved the recovery of the lining of the right dorsal colon after it had lost its blood supply and decreased the amount of toxin leaking across it. Therefore giving lidocaine to horses with a twisted colon during and after colic surgery may be justified based on these findings.

Title: The effect of lidocaine on mucosal healing following ischemic injury of the equine large colon

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INTRODUCTION

Colic is a leading cause of death in horses, with an overall fatality rate of 11% (1). In particular, colic due to large colon volvulus (LCV) has an alarmingly high fatality rate of 30-50% (2, 3). Mortality is highest in the first ten days following surgical correction and has improved little despite advances in intensive therapy. The key to improving postoperative survival of horses with LCV is to hasten repair of the injured colonic mucosa which is a critical barrier between endotoxin in the intestinal lumen and the systemic circulation. One proposed method of hastening repair of damaged intestional mucosa has been the use of intravenous Lidocaine for its novel anti-inflammatory properties. We previously showed Lidocaine to be effective in hastening the repair of ischemic-damaged equine jejunum (4). However, it is unknown whether Lidocaine has the same effect in the large colon and we hypothesize *that Lidocaine will ameliorate the effects of ischemic injury in the equine large colon.*

MATERIALS & METHODS

Horses

All procedures were approved by the Michigan State University Institutional Animal Care and Use Committee. Twelve horses of both sexes were used. The horses used for this non-recovery study were donated to Michigan State University for research purposes. At the time of donation, owners were informed of the details surrounding this project and had the freedom to withdrawal their horse from the study. A majority of the horses used in this study had chronic lameness issues and did not have a good quality of life. Horses had no history of gastrointestinal tract problems and were quarantined for 2 weeks prior to surgery. Results of physical examinations performed prior to surgery were within reference limits. Horses were housed in individual stalls with hay and water available at all times.

Treatments

Each horse was randomly assigned to 1 of 2 groups (n = 6 horses/group). The control group received IV administration of Lactated Ringer's Solution (LRS) at 0.065mL/kg loading dose, followed by 500mL/ hour constant rate infusion. The treatment group received IV administration of Lidocaine at 1.3 mg/kg loading dose, followed by 0.05mg/Kg/ min constant rate infusion.

For both groups of horses, the CRI was stopped at the end of surgery; after the horses had recovered from anesthesia (approx 2 hours after the end of surgery), the CRI was restored. The control group received IV administered LRS (0.065mL/kg) as a bolus over a 15-minute period followed by CRI of 500mL/hr. The treatment group received IV administered Lidocaine (1.3 mg/kg) as a bolus over a 15-minute period followed by CRI (0.05 mg/kg/min).

Monitoring

Physical exam parameters including heart rate, respiratory rate, and temperature were measured before and after surgery. In addition to physical exam parameters, the horse's pain score was quantified using a behavioral scoring system specific for signs of colic (5). Time points included measurements before surgery and 4, 8, and 18 hours after surgery.

Surgical Procedure

Prior to anesthesia, a 14 g. catheter was placed in the left jugular vein following aseptic preparation of the skin. Butorphanol (0.05 mg/kg, IV) was administered to provide analgesia every 6 hours until the time of euthanasia. The horse was sedated with xylazine (1 mg/kg, IV), anesthetized with ketamine (3 mg/kg, IV) and diazepam (0.1 mg/kg, IV), and positioned in dorsal recumbency. The horse was intubated and anesthesia was maintained by use of isoflurane in oxygen. The loading dose of LRS or Lidocaine was administered over 10 minutes, immediately after the horse was placed on gas anesthesia and was maintained at the constant rate infusion.

Following aseptic preparation of the surgical site, a midline 20cm celiotomy was performed and the ascending colon was exteriorized. Two 20cm ischemic sections of large colon were created, one in the right dorsal colon and one at the pelvic flexure, by cross-clamping the intestine with colon clamps and temporarily occluding the vascular supply for 1 hour. At the end of the ischemic period, four full-thickness, wedge-shaped biopsies approximately 3-cm-long were obtained. Two biopsies were created in the right dorsal colon, one within the ischemic region and one adjacent to the colon clamp in the non-ischemic region. The other two biopsies were created in the pelvic flexure region, one within the ischemic region and one adjacent to the colon clamp in the non-ischemic region. The biopsies were obtained for histopatholgy to ensure the degree of injury across horses was the same. Following 1 hour of ischemia, the colon and vascular clamps were removed and the abdomen was closed routinely.

After recovery from anesthesia, the horses were returned to their stall and an additional loading dose of Lidocaine or equivalent volume of LRS was given prior to recommencing the constant rate infusion. Horses were monitored carefully for pain using an established equine behavioral pain scoring system (5). Eighteen hours after the end of the ischemic period, each horse was euthanatized by use of sodium pentobarbital (100 mg/kg, IV) and the colon where the biopsies had been created were immediately harvested.

Ussing Chambers

The mucosa was stripped from the harvested colon and emersed in oxygenated (95% oxygen and 5% carbon dioxide) equine Ringer's solution. Ischemic-injured and non-ischemic injured mucosal samples from the right dorsal colon and pelvic flexure were mounted in 3.14-cm_2 aperture Ussing chambers. Tissues were bathed on the mucosal and serosal sides with 10mL of oxygenated equine Ringer's solution. In addition, the solution used for the serosal side contained 10 mmol of glucose/L, and the solution used for the mucosal side was osmotically balanced by the addition of 10 mmol of mannitol/L. The bathing solutions were circulated and maintained at 37°C by use of water-jacketed reservoirs. After a 15-minute equilibration period, the potential difference (PD) was measured by use of Ringer-agar bridges connected to calomel electrodes, and the short circuit current (I_{sc}) was measured by use of an automated voltage clamp. Electrical measurements were recorded every 15 minutes for 3 hours. The transelectrical resistance (TER) was calculated from the I_{sc} and PD by use of Ohm's law.

RESULTS

Monitoring

Horses treated with either LRS or Lidocaine had higher pain scores 4 hours after surgery, compared with scores for horses in that group before surgery (Figure 1a). However after 4 hours, pain scores for both groups of horses remained elevated at 8 and 18 hours post surgery. Pain scores of horses treated with Lidocaine were not significantly different at any time point from scores of horses treated with LRS.

Measured physical exam parameters including heart rate, respiratory rate, and temperature are plotted in Figure 1b, 1c, and 1d respectively. For each measured physical exam parameter, horses treated with either LRS or Lidocaine had higher values 4 hours after surgery compared to values for horses in that group before surgery. Heart rate increased for both groups of treated horses after surgery and remained elevated up until the time of euthanasia. Lidocaine treated horses did not exhibit a difference in heart rate from horses treated with LRS. As for respiratory rate, the individual variability for both groups of horses was greatest at 4 and 18 hours post surgery for both groups of horses. However, there was no effect of Lidocaine across time points for respiratory rate. Measured temperature increased 4 hours after surgery and remained elevated for both groups of treated horses up until the time of euthanasia. Although temperature increased after surgery, at no point did it exceed the normal physiologic range.

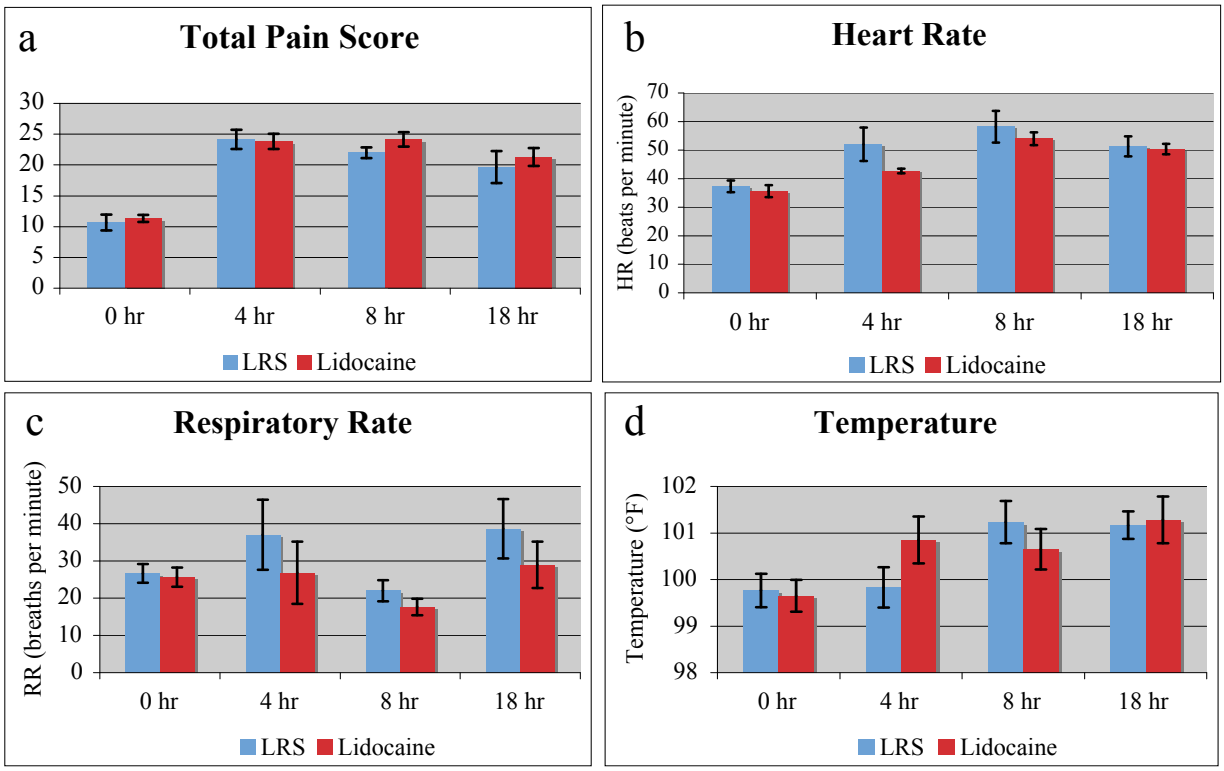

FIGURE 1.

Mucosal Healing

The TER did not differ significantly for the non-ischemic sections of pelvic flexure treated with either LRS or Lidocaine (Figure 2). There was also no significant difference in TER of ischemic-injured mucosa from horses treated with Lidocaine and control sections of pelvic flexure treated with LRS. The ischemic-injured pelvic flexure sections treated with LRS were not significantly different than the non-ischemic sections of pelvic flexure treated with LRS. Even though horses treated with Lidocaine showed an improvement in barrier function in the ischemic region of the pelvic flexure, it was not significant over horses treated with LRS.

With respect to the right dorsal colon, the TER for the non-ischemic regions did not differ significantly between horses treated with Lidocaine or LRS (Figure 3). However there was a significant difference detected between horses treated with LRS or Lidocaine in the ischemic sections of the right dorsal colon ($P=0.035$). Control horses treated with LRS showed a decrease in TER in the ischemic region of the right dorsal colon compared to horses treated with Lidocaine. Horses treated with Lidocaine showed a significant improvement in TER and Lidocaine was able to restore TER back to the level of the non-ischemic injured regions of the right dorsal colon.

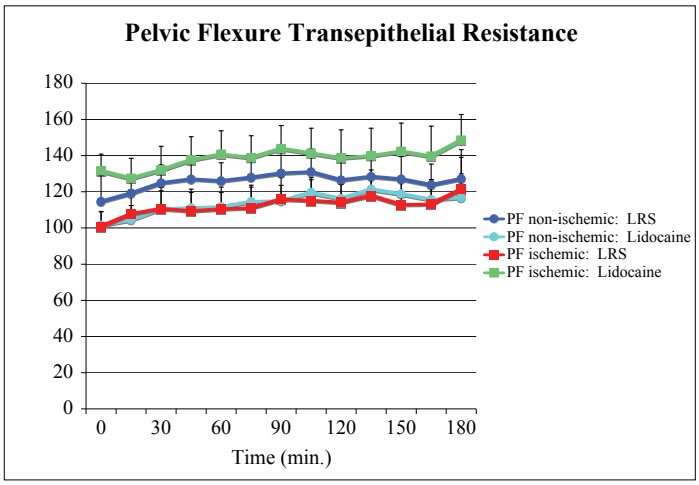

FIGURE 2.

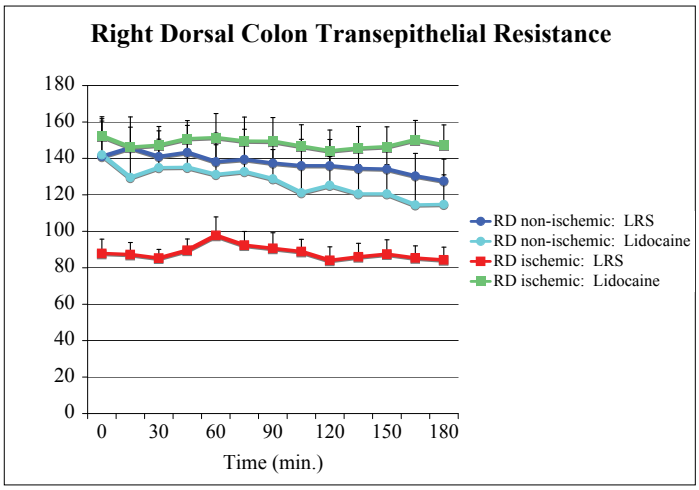

FIGURE 3.

CONCLUSION

Intravenous Lidocaine is often administered to postoperative LCV patients in an effort to improve outcome. However there is no objective information to support or refute this treatment until this study. This study found Lidocaine to be a poor visceral analgesic, but we did find Lidocaine to have a positive effect in the ischemic-injured right dorsal colon. We were not surprised that Lidocaine had no effect on reducing pain scores and reducing physical exam parameters, as this is consistent with previous reports (6). The major finding of this study was the ability of Lidocaine to restore the mucosal barrier function of the ischemic-injured right dorsal colon back to non-ischemic levels. While this was a very exciting result, we were puzzled as to why horses treated with LRS did not have a lower mucosal barrier function in the ischemic-injured pelvic flexure region. Perhaps the right dorsal colon is more sensitive to ischemic damage than the pelvic flexure or Lidocaine is having a different local effect the right dorsal colon compared to the pelvic

flexure region. Although the degree of ischemic-injury in both sampled areas of the colon were not the same, it is consistent with what is seen intraoperatively during exploratory colic surgery of the large colon. For unknown reasons, equine surgeons observe a greater degree of injury in the right dorsal colon than anywhere else in a strangulating lesion of the large colon. For this reason, administering intravenous Lidocaine to LCV patients may help to hasten repair of ischemic-injured right dorsal colon and improve postoperative outcome.

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THE EFFECT OF LIDOCAINE ON MUCOSAL HEALING FOLLOWING ISCHEMIC INJURY OF THE EQUINE LARGE COLON

Kristine Cox, Susan Holcombe, Lorraine Sordillo and Vanessa Cook, Department of Large Animal Clinical Sciences, College of Veterinary Medicine, Michigan State University

Large colon volvulus (LCV) is the leading cause of death among horses with colic. Even after surgical correction, postoperative morbidity and mortality remain high because the injured colon is rarely resected and a large surface area of damaged mucosa remains *in situ*. Therefore, the key to improving postoperative survival in LCV patients lies in repairing the ischemic-injured mucosa. One proposed method of improving mucosal healing has been the use of intravenous lidocaine for its novel anti-inflammatory properties. While lidocaine has been shown to hasten ischemic-injured equine jejunum, it is unknown whether lidocaine has the same effect in the large colon. *It is our hypothesis that lidocaine will ameliorate the effects of ischemic injury in the equine large colon.* To determine the effects of lidocaine in the large colon, 12 horses were separated into two groups (n=6/group) and underwent surgery to restrict blood flow to a portion of the colon for one hour. During surgery, horses received intravenous LRS or lidocaine (loading dose 1.3 mg/kg & CRI 0.05 mg/kg/min). Pain scores were recorded before surgery and 4, 8, and 18 hours post-surgery. Subsequently, horses were euthanized and sections of ischemic and healthy colon were removed and mounted onto Ussing chambers. To determine mucosal integrity, transepithelial resistance of the mucosa was measured. Results suggest lidocaine does not improve pain scores however, lidocaine improved mucosal repair but only in the right dorsal colon. We hope that these results will improve the postoperative survival of horses with LCV. This project was funded by the United States Equestrian Foundation.

May 2, 2013

Sent Via Email: vcook@cvm.msu.edu

Dear Dr. Cook:

I am pleased to inform you that your scientific abstract entitled ***abs: Lidocaine in Equine Large Colon Ischemia*** has been accepted for podium presentation at the 2013 ACVS Veterinary Symposium in the ***Basic and Clinical Advances in Equine Surgical Gastroenterology*** seminar. Your final schedule including the date and time of your presentation will be sent to you via email no later than May 10.

You will have 12 minutes for set-up and presentation (strictly enforced) and 3 minutes for questions and discussion. The seminar room will be equipped with a computer running PowerPoint software, an LCD video/data projector connected to the laptop, one screen, a pointer, microphone and podium. Closer to the meeting you will receive information as to where and when you should plan to load your presentation on to the computer.

Even though you are officially on the program of the 2013 ACVS Veterinary Symposium, you are required to register and pay the appropriate registration fee for the meeting. *This does not apply to you if you are also presenting a seminar lecture at the Symposium.* You are not required to submit *Proceedings* Notes, your short abstract will be used as the written portion of your presentation.

Thank you for submitting your paper to the 2013 ACVS Veterinary Symposium. We look forward to seeing you this fall.

Sincerely,

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