Effect of carboxymethylcellulose and hyaluronate solutions on jejunal healing in horses

Randy B. Eggleston, DVM; P. O. Eric Mueller, DVM, PhD; Anna K. Parviainen, DVM; Erin S. Groover, DVM

Objective—To compare a double-layer inverting anastomosis with a single-layer appositional anastomosis, coated with either 1% sodium carboxymethylcellulose (SCMC) or 0.4% sodium hyaluronate (HA) solutions, in the small intestine of horses with respect to anastomotic healing and adhesion formation.

Animals—18 adult horses.

Procedure—Midline celiotomy and end-to-end jejunal anastomoses were performed. In control group horses (n = 6), a double-layer inverting anastomosis coated with sterile lactated Ringer's solution was performed. In treatment group horses, a single-layer appositional anastomosis was performed that was coated with 1% carboxymethylcellulose solution (SAA + SCMC group horses, 6) or 0.4% hyaluronate solution (SAA + HA group horses, 6). An additional 500 mL of the respective treatment solution was applied to the jejunal serosal surface, and 2 jejunal serosal abrasion sites were created. Horses were euthanatized 10 days after surgery. Anastomoses and abdominal adhesions were evaluated grossly. Anastomotic healing was evaluated on the basis of bursting wall tension.

Results—Bursting wall tension was significantly greater in SAA + SCMC group horses, compared with control group horses. All intestinal segments failed at a point distant to the anastomosis. Significantly fewer adhesions were found at the abrasion sites of SAA + HA group horses, compared with control group horses. No differences were found in adhesion formation at the anastomotic sites among groups.

Conclusions and Clinical Relevance—Coating a single-layer appositional jejunal anastomosis with SCMC or HA solutions does not adversely affect anastomotic healing. Application of 0.4% HA solution to the serosal surface of the jejunum significantly decreases the incidence of experimentally induced intra-abdominal adhesion formation in horses. (*Am J Vet Res* 2004;65:637–643)

Surgical intervention of small intestinal disease requiring resection and anastomosis is becoming more commonplace as a result of earlier recognition of the disease and advances in surgical and anesthetic techniques. Common problems associated with small intestinal diseases in horses include intra-abdominal adhesions, anastomotic complications, ileus, and peritonitis.[1-6] Survival rates of these patients have improved substantially over the past 2 decades but remain disappointingly low. The reported short-term survival rate, as defined by discharge from the hospital, is from 49% to 85%.[2,3,7,a] The long-term survival rate, as defined within a range of 7 months to 1 year, is from 24% to 73%.[3,6-8,a] In 1 study,[3] 19% of surgeries involving the small intestine required a repeat celiotomy as a result of early postoperative complications. Formation of intra-abdominal adhesions requiring either additional surgery or euthanasia may occur in up to 22% of horses undergoing surgery for primary small intestinal disease.[1]

Numerous treatments aimed at minimizing abdominal adhesions have been evaluated in humans, laboratory animals, sheep, ponies, and horses.[9-19] Only a limited number of these treatments have been evaluated for use in abdominal surgery in horses.[13,14,16,17,19] It has been shown that **sodium carboxymethylcellulose (SCMC)** solution, a high molecular-weight hydrophilic polysaccharide polymer solution, significantly decreased abdominal adhesions in mice, rats, ewes, ponies, and horses.[15,16,20-24] Precoating of serosal surfaces prior to intestinal manipulation results in more favorable results than serosal coverage after manipulation.[25-27] Recent reports indicate that SCMC solution decreases the incidence of intra-abdominal adhesions in horses with no adverse effect on incisional wound healing, postoperative complications, or short- and long-term survival.[16,20,21]

Sodium hyaluronate (HA) is a naturally occurring hydrophilic anionic polysaccharide polymer found in all tissues and, more notably, in connective tissue, skin, cartilage, synovial fluid, and vitreous. It is a major component of the extracellular matrix.[28] It has been shown to significantly decrease abdominal adhesions in humans when in a 0.4% solution or combined with SCMC as a bioresorbable membrane.[9,10] In horses, an HA-SCMC membrane has been shown to significantly decrease experimentally induced abdominal adhesions[17,19] without adversely affecting anastomotic wound healing.[19,21]

Single-layer appositional anastomoses have not gained favor in equine small intestinal surgery because they have been associated with severe perianastomotic adhesion formation and decreases in luminal and stomal diameters resulting from extramural distortion of the intestine.[29,30] However, when a single-layer appositional anastomosis was performed in combination with an HA-SCMC membrane, the incidence of adhesion formation was similar to that of the commonly performed double-layer inverting technique.[19]

Received April 23, 2003.
Accepted September 16, 2003.
From the Departments of Large Animal Medicine (Eggleston, Mueller, Groover), College of Veterinary Medicine, University of Georgia, Athens, GA 30602; and Dunkirk Animal Hospital, Dunkirk, MD 20754 (Parviainen).
Supported by a grant from the University of Georgia Veterinary Medical Experimental Station.
Abstract presented at the 11th Annual American College of Veterinary Surgeons Veterinary Symposium, Chicago, October 2001.
The authors thank Deanne King for technical assistance.
Address correspondence to Dr. Eggleston.

Objectives of the study reported here were as follows: 1) to compare 3 hand-sutured jejunal anastomotic techniques (**double-layer inverting pattern [DIA]**, **single-layer appositional pattern [SAA]** coated with SCMC solution, and SAA coated with HA solution) with respect to anastomotic healing and perianastomotic adhesion formation, and 2) evaluate the effect of precoating of the small intestine with an HA solution in preventing experimentally induced intra-abdominal adhesions. We hypothesized that application of SCMC or HA solutions to a single-layer appositional jejunal anastomosis would provide a safe and reliable method for performing small intestinal anastomoses in horses. Secondly, although SCMC solution has been previously shown to significantly decrease experimentally induced adhesion formation,[16,20,23,31] we hypothesize that precoating serosal surfaces with a 0.4% HA solution would significantly minimize experimentally induced adhesion formation.

Materials and Methods

Experimental protocol—Eighteen healthy adult horses ranging in age from 2 to 17 years (mean, 9 years) and weighing between 395 and 610 kg (mean, 470.5 kg) were used in the study. An institutional animal care and use committee approved experimental procedures and animal care. Horses were housed in stalls, fed alfalfa hay and a pelleted feed twice daily, and offered water free choice. Horses were randomly assigned to 3 experimental groups as follows: DIA (control) group horses (n = 6) in which a jejunal anastomosis was performed with a DIA, SAA + SCMC group horses (6) in which a jejunal anastomosis was performed with a SAA and coated with SCMC solution, and SAA + HA group horses (6) in which a jejunal anastomosis was performed with a SAA and coated with HA solution.

Preparation of SCMC and HA solutions—A 1% wt/wt solution of SCMC was prepared by adding boiling, sterile water to 10 g of SCMC powder[b] to bring the total volume to 1 L. The SCMC solution was then transferred into 1-L glass bottles and autoclaved at 121°C for 20 minutes. The shelf life of SCMC solution was 60 days. Sterile, nonpyogenic 0.4% wt/wt HA solution[c] was prepared in a pH 7 isomolar PBS solution.

Surgical procedures—Food was withheld for 12 hours before surgery. One hour before induction of anesthesia, potassium penicillin G (22,000 IU/kg, IV, q 6 h), gentamicin sulfate (6.6 mg/kg, IV, q 24 h), and flunixin meglumine (1.1 mg/kg, IV, q 12 h) were administered. Each horse was anesthetized with xylazine hydrochloride (1.1 mg/kg, IV), followed by ketamine hydrochloride (2.2 mg/kg, IV) and maintained with sevoflurane in oxygen. Lactated Ringer's solution (10 mL/kg/h, IV) was administered during the surgical procedure. Horses were positioned in dorsal recumbency, and the ventral midline was prepared for aseptic surgery.

A 25-cm long ventral midline celiotomy and systematic abdominal exploratory was performed. If adhesions or anatomic abnormalities were identified, horses were not used in the study. The entire jejunum was then exteriorized, examined, and run from the ileocecal orifice to the duodenocolic ligament. The DIA group horses served as controls, and 1 L of sterile saline (0.9% NaCl) solution was used to lubricate the intestine during manipulation. In treatment horses, 1 L of SCMC solution (SAA + SCMC group) or HA solution (SAA + HA group) was used to lubricate the intestine during manipulation and completely cover each anastomosis. Intra-abdominal adhesions were induced in all horses at 2 locations by use of a method of serosal trauma described previously.[20,32] Briefly, two 6 × 4-cm areas of the antimesenteric border of the jejunum, 4 and 12 m proximal to the ileocecal junction, were briskly rubbed 100 times with a dry sterile gauze. Three simple interrupted seromuscular 2-0 chromic catgut[d] sutures were then placed 2 cm apart in the abraded area.

In all horses, an end-to-end jejunal anastomosis was performed 10 meters proximal to the ileocecal orifice. A 1-m length of jejunum was isolated from the abdomen with moistened sterile towels, and the jejunum was incised perpendicular to the mesenteric border.

In DIA group horses, a double-layer, end-to-end inverting anastomosis was performed. The mucosa-submucosa layer was apposed with 3-0 polydioxanone[e] by use of a simple continuous pattern. The seromuscular layer was inverted with 3-0 polydioxanone by use of a continuous Cushing pattern. Each suture line was interrupted and tied at the mesenteric and antimesenteric borders to prevent a purse-string effect. At completion of the anastomosis, the site was lavaged with sterile lactated Ringer's solution before replacing the intestinal segment back into the abdomen.

In SAA + SCMC group horses, a single-layer, end-to-end, appositional anastomosis was performed. The mucosa, submucosa, and seromuscular layers were apposed with a simple continuous suture pattern with 3-0 polydioxanone. The mucosa was meticulously folded below the seromuscular layer with each throw to minimize mucosal exposure. The suture line was interrupted and tied at the mesenteric and antimesenteric borders. At completion of the anastomosis, the site was lavaged with sterile lactated Ringer's solution before liberally coating the anastomosis with sterile 1% SCMC solution and replacing the intestinal segment back into the abdomen.

In SAA + HA group horses, a single-layer, end-to-end, appositional anastomosis was performed as in SAA + SCMC group horses. Once the anastomosis was complete, the site was lavaged with sterile lactated Ringer's solution before liberally coating the anastomosis with sterile 0.04% HA solution. The intestinal segment was placed back into the abdomen and the ventral midline incision closed routinely.

Postoperative care and monitoring—After recovery, horses were allowed access to water ad libitum and were gradually returned to full feed during the next 36 hours. Treatment with antibiotics and flunixin meglumine was continued for 48 hours. Each horse was monitored every 6 hours for food consumption, pulse and respiratory rate, rectal temperature, signs of abdominal pain, fecal output, and swelling or drainage associated with the incision. After the initial 48-hour postoperative period, the monitoring interval was increased to every 12 hours. Any horse that had clinical signs of abdominal pain after surgery was examined and treated appropriately. Horses were housed in individual stalls for 10 days after surgery.

Necropsy examination—Horses in all groups were euthanized by administration of an overdose of pentobarbital sodium solution (87 mg/kg, IV) 10 days after surgery. The abdominal incision, peritoneal cavity, anastomoses, and all abdominal organs were evaluated. The presence of intra-abdominal adhesions was recorded as "yes" or "no." If adhesions were present, they were further described as to their location and severity. Adhesions were designated as fibrinous if they could easily be pulled apart or fibrous if they could not be pulled apart without tearing the serosa. Each anastomosis, including 7 cm of jejunum proximal and distal to the anastomosis, was harvested for determination of intestinal bursting pressure.

Bursting wall tension determination—Intestinal bursting wall tension was used as a biomechanical indicator of

anastomotic strength.[33,34] A 14-cm-long segment of jejunum containing the anastomosis was lavaged with saline solution to remove all intestinal contents. Each segment was coded to conceal the identity of the donor horse and the treatment used. Intestinal segments were submersed into a glass chamber containing saline solution (**Fig 1**). The segment of intestine was distended with air delivered at a constant rate of 0.5 L/min until bursting was evident by the appearance of air bubbles within the fluid chamber or rupture and abrupt collapse of the intestinal segment corresponding to an abrupt drop in the recorded tracing. Fluid displaced from the fluid chamber during intestinal distention was collected in a graduated cylinder and the volume recorded for later calculations. Pressure within the intestinal segment was recorded continuously on a chart recorder[f] from a pressure transducer[g] attached to the tubing delivering air to the intestinal segment. The maximum pressure at the time of bursting was recorded as the bursting pressure (mm Hg). Bursting wall tension was then calculated by use of Laplace's law as follows:

$$BWT = BP \times r$$

where BWT is bursting wall tension, BP is bursting pressure (dynes/cm^2) at the time of rupture, and r is the radius of the intestinal segment. The radius was calculated, assuming the intestinal segment approximated a cylinder by use of the following equation:

$$r = \sqrt{(v/\pi l)}$$

where v is the volume (mL) of fluid displaced during intestinal distention, and l is the length of the intestinal segment.

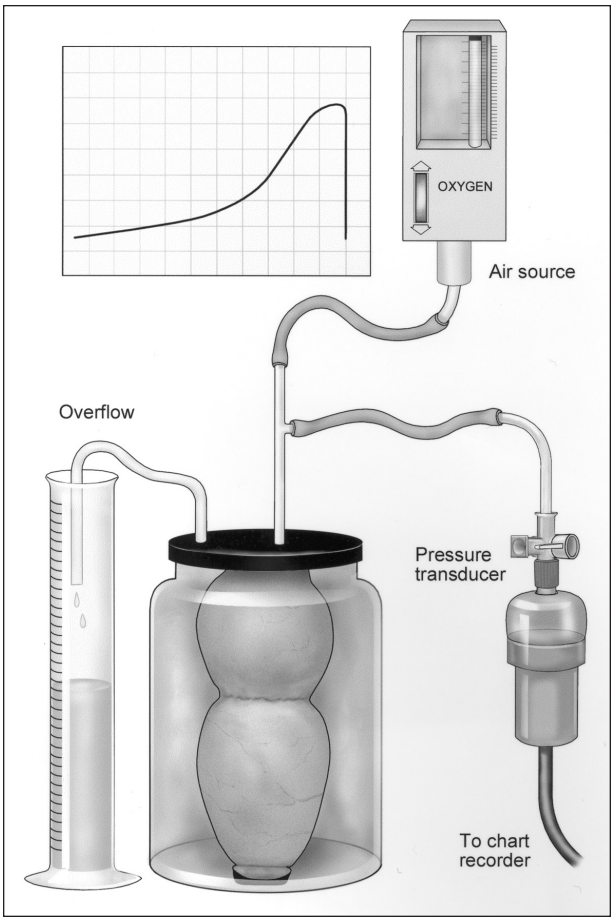

Figure 1—Diagram of the apparatus used to measure bursting pressure of intestinal segments. A 14-cm intestinal segment containing the anastomosis was occluded at each end and secured in a fluid chamber. Oxygen was infused into the proximal end of the intestinal segment at a controlled rate. An in-line pressure transducer connected to a calibrated physiographic recorder was used to measure intraluminal pressure. As the segment was inflated, fluid from the fluid chamber was displaced and collected in a graduated cylinder to be used for intestinal radius calculations $r = \sqrt{(v/\pi l)}$. Pressures were recorded continuously until intestinal rupture, indicated by the presence of air bubbles in the fluid chamber or abrupt intestinal collapse and deflection of the pressure tracing. Using the LaPlace's law, bursting wall tension (dynes/cm) was calculated from the collected data by use of the following equation:

$$BWT = P \times r$$

where P is bursting pressure at the time of intestinal failure and r is the radius.

Statistical analysis—The frequency of intra-abdominal adhesion formation between control and treatment groups was compared by use of a χ^2 test for independence. Age, weight, and mean intestinal bursting tension among groups were compared with an ANOVA. Significant differences of means between groups were compared with a Fischer protected least significant difference test for multiple comparisons. Statistical significance was established at a value of $P < 0.05$.

Results

Significant differences regarding age or weight were not detected among groups ($P = 0.63$ and 0.30, respectively). Hematologic and serum biochemical values in blood samples obtained before surgery from all horses were within reference ranges for our laboratory. All horses recovered from surgery without complications.

Two control horses and 1 horse from the SAA + SCMC group had a single episode of colic after surgery that responded to medical treatment consisting of nasogastric intubation and a single dose of flunixin meglumine (500 mg, IV). A second horse from the SAA + SCMC group had a prolonged episode of colic 2 days after surgery and was treated medically consisting of flunixin meglumine (500 mg, IV) and nasogastric intubation. Twenty-four hours after treatment, the horse again had signs of abdominal pain and was treated with a second dose of flunixin meglumine (500 mg, IV), nasogastric intubation, and IV administration of fluids. Abdominal palpation per rectum revealed multiple loops of moderately distended small intestine. The horse continued to have signs of abdominal pain despite medical treatment. As a last effort, a single dose of neostigmine (2 mg, SC) was administered. Thirty minutes following neostigmine administration, the horse became comfortable and a repeat abdominal palpation per rectum revealed complete resolution of the small intestinal distension. The horse resumed consumption of hay and water the following day and had no further complications throughout the study.

Gross necropsy examination revealed normal healing of all anastomoses. No evidence of anastomotic leakage, abscess formation, or stricture at any of the anastomoses was found. In 1 control horse, an omental adhesion formed from an abrasion site to a distal segment of jejunum. A single loop of jejunum was contained within the omental loop. No evidence of obstruction or strangulation of the incarcerated intestine was found. The jejunum at the abrasion sites was

Table 1—Mean (± SD) values of bursting pressure (BP) and bursting wall tension (BWT) in jejunal segments from horses following a double-layer inverting anastomosis (control group horses, n = 6), a single-layer appositional anastomosis coated with sodium carboxymethylcellulose solution (SAA + SCMC group horses, 6), or a single-layer appositional anastomosis coated with hyaluronate solution (SAA + HA group horses, 6)

Groups	BP* (mm Hg)	BP* (dynes/cm$^{2)}$	BWT (dynes/cm)
Control	282.50 ± 63.70	376,636 ± 84,924	879,539 ± 142,854[a]
SAA + SCMC	319.00 ± 129.49	425,298 ± 172,638	1,416,670 ± 608,541[b]
SAA + HA	311.00 ± 33.24	414,632 ± 44,318	954,255 ± 161,997
SCMC + HA	315.00 ± 89.23	419,965 ± 118,957	1,185,462 ± 485,436

*1 mm Hg = 1,333.22 dynes/cm^2.
[a,b]Values with different superscript letters differ significantly ($P < 0.05$).
SCMC + HA = Combined data from treatment groups (SAA + SCMC and SAA + HA group horses).

thickened and had focal areas of serosal hemorrhage associated with the serosal trauma. No abnormalities were evident throughout the remainder of the abdominal cavity.

Anastomotic healing—Mean bursting wall tension was significantly ($P = 0.029$) greater in SAA + SCMC group horses, compared with control group horses (**Table 1**). Comparison of the treatment groups combined (SCMC and HA) to the control group did not reveal a significant ($P = 0.16$) difference in bursting wall tension. Bursting pressures were not obtained from 1 horse from each the SAA + SCMC and SAA + HA groups as a result of complications with harvesting of intestinal segments. Failure of the intestinal segments occurred at a site distant to the anastomosis in all horses.

Adhesion formation—All 6 control group horses developed mature, fibrous intra-abdominal adhesions. Adhesions were associated with both abrasion sites in 5 of 6 control group horses. Among these 5 control group horses, 2 had adhesions between the abrasion site and a distant segment of jejunum. The remaining 3 control group horses had adhesions between the abrasion sites and the adjacent mesentery. Adhesions ranged in length from 4 to 9 cm at the abrasion sites. Four of 6 control group horses also had adhesions associated with the anastomosis; 1 horse had an omental adhesion, whereas 3 horses had adhesions to the adjacent mesentery. Anastomotic involvement ranged from 1 to 3 cm in length to approximately 90% of the total circumference of the anastomosis. None of the adhesions resulted in distortion or stricture of the intestinal lumen.

Three of 6 SAA + SCMC group horses developed mature, fibrous intra-abdominal adhesions. Two of these 3 horses developed omental adhesions to a single abrasion site ranging in length from 2 to 9 cm. Mesenteric adhesions were associated with the anastomosis in 2 SAA + SCMC group horses, ranging from 2 cm in length to 50% involvement of the anastomotic circumference. The SAA + SCMC group horse that had 50% involvement of the anastomosis was the same horse that had persistent signs of colic 2 days after surgery. No stricture or distortion of the intestine was observed.

Three of 6 SAA + HA group horses developed mature, fibrous intra-abdominal adhesions. One horse had an omental adhesion to a single abrasion site. The remaining 2 SAA + HA group horses had small 1 cm-long adhesions involving the anastomosis, 1 to the omentum and the other to the adjacent mesentery. Significantly ($P = 0.021$) fewer abrasion site adhesions were found in SAA + HA group horses, compared with control group horses. The incidence of adhesion formation at the anastomoses was not significantly different among groups.

Discussion

Results of studies[33,34] evaluating incisional strength and intestinal healing have revealed anastomotic strength to be weakest at 3 to 7 days after surgery and highly dependent on suture strength during early healing. Between 7 to 14 days, the anastomosis rapidly gains strength corresponding with a rapid increase in collagen content.[35-37] By 7 and 14 days, the anastomosis is equal to or greater than the adjacent intestine.[36,38]

Bursting strength is the combined tensile strength and stretch of a material as measured by the ability of the material to resist rupture when pressure is applied at a constant rate. Bursting pressure is the measured intraluminal pressure at the time of rupture of the intestinal segment. Bursting pressure does not take into account volume, length, or radius of the intestinal segment.[34,39,40] Bursting wall tension is calculated by use of Laplace's law, which states that as the radius of a distensible cylinder increases, the wall tension required to withstand a given internal fluid pressure increases correspondingly.[34,41] Bursting wall tension more accurately reflects anastomotic strength and was used in this study as a biomechanical indicator of anastomotic strength and quality of healing.

In our study, application of SCMC or HA solutions to the serosal surface of the jejunum prior to and after formation of the single-layer appositional anastomosis did not adversely effect anastomotic healing as indicated by the bursting wall tension. A significant ($P = 0.029$) increase was found in the bursting wall tension in SAA + SCMC group horses, compared with control group horses. No significant difference in bursting wall tension was found between control group horses and SAA + HA group horses or between the 2 treatment groups. Sodium carboxymethylcellulose has been previously shown to have no adverse effects on anastomotic healing when used with a double-layer inverting anastomotic technique.[21] The reason for the significantly higher bursting wall tension of SAA + SCMC group horses in our study is not clear. Keeping in mind

that all specimens failed at sites other than the anastomosis, the higher bursting wall tension of SAA + SCMC group horses is most likely not clinically important. In a recent study[42] evaluating 2 stapled anastomotic techniques, the bursting pressure and bursting wall tension of normal intact jejunum measured 200.41 ± 14.17 mm Hg and 827,037 ± 59,565 dynes/cm, respectively. In our study all jejunal segments including the double-layer inverting and single-layer appositional anastomoses sustained pressures above that of the normal intact jejunum.

It has been shown that single-layer appositional anastomotic techniques are associated with increased risks and development of perianastomotic adhesions.[30,44,45] Increased risks arise from exposure of intestinal mucosa, exposure of suture material, and leakage at the anastomotic site resulting in contamination of the serosal surface.[19,29,30,44,45] Use of a double-layer inverting anastomotic technique helps to decrease the risk of perianastomotic adhesions by allowing for complete coverage of the mucosa and creation of a tight serosal seal. More recently in our laboratory we demonstrated that the use of a simple continuous single-layer appositional anastomotic technique used in combination with a bioresorbable HA membrane compared similarly with the double-layer technique in relation to perianastomotic adhesion formation. Performing the single-layer technique alone resulted in a significant increase in adhesion formation.[19]

In our study, the addition of HA or SCMC solutions with a single-layer appositional anastomosis did not significantly decrease the formation of perianastomotic adhesions, compared with a double-layer inverting anastomotic technique. The single-layer appositional anastomotic technique has been demonstrated to produce a significantly greater anastomotic stomal diameter than double-layer inverting techniques.[19] However, results of our study revealed that the addition of HA or SCMC solutions to the single-layer anastomosis did not significantly decrease the risk of anastomosis associated adhesions, compared with a double-layer inverting anastomotic technique. Therefore, the authors cannot recommend the use of HA or SCMC solutions to facilitate single-layer appositional anastomoses in horses. Results of a previous study[19] performed in our laboratory support the use of a bioresorbable SCMC-HA membrane to facilitate single-layer appositional anastomosis and minimize adhesion formation. Although a direct comparison between the use of a SCMC-HA membrane and SCMC or HA solutions to facilitate single-layer anastomoses in horses has not been performed, it is the authors' opinion that use of an bioresorbable SCMC-HA membrane is superior to either HA or SCMC solutions in minimizing perianastomotic adhesion formation.

Sodium carboxymethylcellulose and HA solutions have been reported to minimize incidental surgical serosal trauma[22,46,47,h] and separate potentially adhesionogenic serosal surfaces during early postoperative healing. Sodium carboxymethylcellulose solution has been shown to significantly decrease adhesion formation in multiple experimental models.[15,20,23,24,48] To our knowledge, however, the use of HA solution to facilitate small intestinal anastomoses in horses has not been reported. In our study, precoating of serosal surfaces with 0.4% HA solution resulted in a significant (P = 0.021) decrease in experimentally induced adhesion formation, compared with that of control group horses. Although results of several previous studies[20,23,25] have revealed the effectiveness of SCMC solution in minimizing adhesion formation in horses, in our study, HA solution was more efficacious than SCMC solution in preventing adhesion formation.

Manipulation, trauma, or both to serosal and peritoneal surfaces during exploratory celiotomy results in mesothelial damage, peritoneal inflammation, and extravascular fibrin deposition.[49] Normally excessive fibrin is degraded via the fibrinolytic system. Peritoneal inflammation as a result of intestinal ischemia or incidental surgical trauma results in an imbalance between fibrin deposition and fibrin degradation.[50,51] This imbalance, in a large part, is the result of a decrease in tissue-type plasminogen activator and an increase in plasminogen activator inhibitor type 1.[50,52] Results of a study[52] in people indicate that tissue-type plasminogen activator is rapidly released by the visceral peritoneum during laparotomy. Persistent fibrin deposition provides a scaffold for vascular and fibroblast ingrowth leading to the development of mature fibrous adhesions. Separation of potentially adhesionogenic surfaces with high molecular weight solutions, such as SCMC and HA solutions, during the early postoperative period when this imbalance occurs is 1 method of preventing adhesion formation.[15,20,23] Alternate mechanisms of decreased adhesion formation by HA solution have been investigated.[53] Study results reveal the ability of HA solution to alter the fibrinolytic response in tumor necrosis factor-α stimulated human peritoneal mesothelial cells, resulting in decreased plasminogen activator inhibitor type 1 concentrations. Tissue type plasminogen activator concentrations were not significantly affected, although an increase was found in the intracellular tissue-type plasminogen activator concentrations observed.[53]

Another mechanism of adhesion reduction by HA solution may involve interaction with CD44 cell surface receptors. At the cellular level, HA interacts via multiple cell surface receptors. The major receptor for hyaluronan is CD44.[54,55] The CD44 cell surface receptor has recently been found to be present on the equine serosa and peritoneum.[i] Results of an in vitro study[56] have revealed an up regulation of hyaluronan synthase-2 and an increase in hyaluronan synthesis following injury to human peritoneal mesothelial cells. Sodium hyaluronate has also been shown to cause mesothelial proliferation, even in the face of tumor necrosis factor-α, lipopolysaccharide, or both, which may involve mesothelial cell surface CD44 receptors.[57] Hyaluronan has been shown to influence many aspects of tissue healing including activation and modulation of inflammation, free radical scavenger, cell proliferation and migration, angiogenesis, and decreased collagen deposition.[58]

[a]Freeman D, Hammock P, Richter R-A, et al. Short term and long term survival after small intestinal surgery in horses (abstr), in *Proceedings*. 9th Annu Am Coll Vet Surg Symp 1999:7.

[b]Aqualon cellulose gum, Aqualon Co, Wilmington, Del.

[c]SepraCoat, Genzyme Corp, Cambridge, Mass. Supplied by Dr. Lynn Peck and Dr. Eugene P. Goldberg, Biomedical Engineering Center, Department of Materials Science and Engineering, University of Florida, Gainesville, Fla.

[d]Surgical gut suture-chromic, Ethicon Inc, Somerville, NJ.

[e]PDS, Ethicon Inc, Somerville, NJ.

[f]Gould 2400S chart recorder, Gould Instrument Systems Inc, Valley View, Ohio.

[g]P23 ID Gould pressure transducer, Gould Instrument Systems Inc, Valley View, Ohio.

[h]Mueller POE, Eggleston R, Parviainen A. Effect of carboxymethylcellulose and hyaluronate solutions on equine jejunal healing and adhesion formation (abstr). *Vet Surg* 2001;30:502.

[i]Frees K, Gaughan E, Lillich J, et al. The presence of hyaluronan receptors on equine serosa and peritoneum (abstr), in *Proceedings*. 11th Annu Am Coll Vet Surg Vet Symp 2001;7.

References

1. Baxter GM, Broome TE, Moore JN. Abdominal adhesions after small intestinal surgery in the horse. *Vet Surg* 1989;18:409–414.

2. Hunt JM, Edwards GB, Clarke KW. Incidence, diagnosis and treatment of postoperative complications in colic cases. *Equine Vet J* 1986;18:264–270.

3. MacDonald M, Pascoe J, Stover S, et al. Survival after small intestine resection and anastomosis in horses. *Vet Surg* 1989;18:415–423.

4. Parker J, Fubini S, Todhunter R. Retrospective evaluation of repeat celiotomy in 53 horses with acute gastrointestinal disease. *Vet Surg* 1989;18:424–431.

5. Pascoe PJ, McDonell WN, Trim CM, et al. Mortality rates and associated factors in equine colic operations—a retrospective study of 341 operations. *Can Vet J* 1983;24:46–85.

6. Reeves MJ, Hilbert BJ, Morris RS. A retrospective study of 320 colic cases referred to a veterinary teaching hospital, in *Proceedings*. 2nd Equine Colic Res Symp 1986;242–250.

7. Fugaro MN, Cote NM. Survival rates for horses undergoing stapled small intestinal anastomosis: 84 cases (1988–1997). *J Am Vet Med Assoc* 2001;218:1603–1607.

8. Phillips T, Walmsley J. Retrospective analysis of the result of 151 exploratory laparotomies in horses with gastrointestinal disease. *Equine Vet J* 1993;25:427–431.

9. Becker JM, Beck DE, Wolff BG, et al. Prevention of postoperative abdominal adhesions by a sodium hyaluronate-based bioresorbable membrane: a prospective, randomized, double-blind multicenter study. *J Am Coll Surg* 1996;183:297–306.

10. Diamond MP. Reduction of adhesions after uterine myomectomy by Seprafilm membrane (HAL-F): a blinded, prospective, randomized, multicenter clinical study. Seprafilm Adhesion Study Group. *Fertil Steril* 1996;66:904–910.

11. Diamond MP. Reduction of de novo postsurgical adhesions by intraoperative precoating with Sepracoat (HAL-C) solution: a prospective, randomized, blinded, placebo-controlled multicenter study. The Sepracoat Adhesion Study Group. *Fertil Steril* 1998;69:1067–1074.

12. Frishman GN, Peluso JJ, Kratka SA, et al. Preoperative versus postoperative dextran 70 for preventing adhesion formation. *J Reprod Med* 1991;36:707–710.

13. Hague B, Honnas C, Berridge B, et al. Evaluation of postoperative peritoneal lavage in standing horses for prevention of experimentally induced abdominal adhesions. *Vet Surg* 1998;27:122–126.

14. Kuebelbeck K, Slone D, May K. Effect of omentectomy on adhesion formation in horses. *Vet Surg* 1998;27:132–137.

15. Moll H, Wolfe D, Schumacher J, et al. Evaluation of sodium carboxymethylcellulose for prevention of adhesions after uterine trauma in ewes. *Am J Vet Res* 1992;53:1454–1456.

16. Mueller P, Hunt R, Allen D, et al. Intraperitoneal use of sodium carboxymethylcellulose in horses undergoing exploratory celiotomy. *Vet Surg* 1995;24:112–117.

17. Mueller P, Hay W, Harmon B, et al. Evaluation of a bioresorbable hyaluronate-carboxymethylcellulose membrane for prevention of experimentally induced adhesions in horses. *Vet Surg* 2000;29:48–53.

18. Pagidas K, Tulandi T. Effects of Ringer's lactate, Interceed(TC7) and Gore-Tex Surgical Membrane on postsurgical adhesion formation. *Fertil Steril* 1992;57:199–201.

19. Eggleston R, Mueller E, Quandt J, et al. Use of a hyaluronate membrane for jejunal anastomosis in horses. *Am J Vet Res* 2001;62:1314–1319.

20. Moll H, Schumacher J, Wright J, et al. Evaluation of sodium carboxymethylcellulose for prevention of experimentally induced abdominal adhesion in ponies. *Am J Vet Res* 1991;52:88–91.

21. Mueller PO, Harmon BG, Hay WP, et al. Effect of carboxymethylcellulose and a hyaluronate-carboxymethylcellulose membrane on healing of intestinal anastomoses in horses. *Am J Vet Res* 2000;61:369–374.

22. Peck LS, Fossum GT, Goldberg EP. Evaluation of CMC and HA solutions for adhesiolysis. *J Invest Surg* 1995;8:37–348.

23. Hay WP, Mueller PO, Harmon BG, et al. One percent sodium carboxymethylcellulose prevents experimentally induced adhesions in horses. *Vet Surg* 2001;30:223–227.

24. Elkins T, Bury R, Ritter J, et al. Adhesion prevention by solutions of sodium carboxymethylcellulose in the rat I. *Fertil Steril* 1984;41:926–928.

25. Murphy DJ, Peck LS, Detrisac CJ, et al. Use of a high-molecular-weight carboxymethylcellulose in a tissue protective solution for prevention of postoperative abdominal adhesions in ponies. *Am J Vet Res* 2002;63:1448–1454.

26. Yaacobi Y, Israel A, Goldberg E. Prevention of postoperative abdominal adhesions by tissue precoating with polymer solutions. *J Surg Res* 1993;55:422–426.

27. Goldberg E, Burns J, Yaacobi Y. Prevention of postoperative adhesions by precoating tissues with dilute sodium hyaluronate solutions. In: Diamond M, diZerega G, Linsky C, et al, eds. *Gynecologic surgery and adhesion prevention*. New York: Wiley-Liss, 1993;191–204.

28. Fraser JR, Laurent TC, Laurent UB. Hyaluronan: its nature, distribution, functions and turnover. *J Intern Med* 1997;242:27–33.

29. Dean PW, Robertson JT. Comparison of three suture techniques for anastomosis of the small intestine in the horse. *Am J Vet Res* 1985;46:1282–1286.

30. Reinertson E. Comparison of three techniques for intestinal anastomosis in Equidae. *J Am Vet Med Assoc* 1976;169:208–212.

31. Hay W, Mueller P, Harmon B, et al. Effect of intra-peritoneal administration of sodium carboxymethylcellulose on adhesion formation and anastomotic healing in horses, in *Proceedings*. 6th Equine Colic Res Symp 1998;63.

32. Baxter G, Jackman B, Eades S, et al. Failure of calcium channel blockade to prevent intra-abdominal adhesions in ponies. *Vet Surg* 1993;6:496–500.

33. Archer RM, Parsons JC, Lindsay WA, et al. A comparison of enterotomies through the antimesenteric band and the sacculation of the small (descending) colon of ponies. *Equine Vet J* 1988;20:406–413.

34. Nelsen TS, Anders CJ. Dynamic aspects of small intestinal rupture with special consideration of anastomotic strength. *Arch Surg* 1966;93:309–314.

35. Gottrup F. Healing of incisional wounds in stomach and duodenum. Collagen distribution and relation to mechanical strength. *Am J Surg* 1981;141:222–227.

36. Gottrup F. Healing of incisional wounds in stomach and duodenum. Functional interaction between normal and wounded tissue. *Am J Surg* 1981;141:706–711.

37. Stashak TS. Techniques for enterotomy, decompression, and intestinal resection/anastomosis. *Vet Clin North Am Large Anim Pract* 1982;4:147–165.

38. Pascoe J, Peterson P. Intestinal healing and methods of anastomosis. *Vet Clin North Am Equine Pract* 1989;5:309–334.

39. Oakes MG, Hosgood G, Snider TG III, et al. Esophagotomy closure in the dog. A comparison of a double-layer appositional and two single-layer appositional techniques. *Vet Surg* 1993;22:451–456.

40. Radasch RM, Merkley DF, Wilson JW, et al. Cystotomy closure. A comparison of the strength of appositional and inverting suture patterns. *Vet Surg* 1990;19:283–288.

41. Levine SA, Smith DF, Wilson JW, et al. Comparative healing of mesenteric and antimesenteric incisions in the bovine jejunum. *Am J Vet Res* 1988;49:1339–1343.

42. Bickers RJ, Blackford JT, Eiler H, et al. A comparison of the mechanical strength of two stapled anastomosis techniques for equine small intestine. *Vet Surg* 2002;31:104–110.

43. Bristol DG, Cullen J. A comparison of three methods of end-to-end anastomosis in the equine small colon. *Cornell Vet* 1988;78:325–337.

44. Hanson RR, Nixon AJ, Calderwood-Mays M, et al. Evaluation of three techniques for end-to end anastomosis of the small colon in horses. *Am J Vet Res* 1988;49:1613–1620.

45. Mueller POE, Allen D. Instrumentation and techniques in equine gastrointestinal surgery. *Vet Clin North Am Equine Pract* 1996;12:207–233.

46. Leach RE, Burns JW, Dawe EJ, et al. Reduction of postsurgical adhesion formation in the rabbit uterine horn model with use of hyaluronate/carboxymethylcellulose gel. *Fertil Steril* 1998;69:415–418.

47. Burns JW, Skinner K, Colt MJ, et al. A hyaluronate based gel for the prevention of postsurgical adhesions: evaluation in two animal species. *Fertil Steril* 1996;66:814–821.

48. Elkins T, Ling F, Ahokas R, et al. Adhesion prevention by solutions of sodium carboxymethylcellulose in the rat II. *Fertil Steril* 1984; 41:929–932.

49. Holmdahl L. Making and covering of surgical foot prints. *Lancet* 1999;353:1456–1457.

50. Holmdahl L, Eriksson E, Eriksson BI, et al. Depression of peritoneal fibrinolysis during operation is a local response to trauma. *Surgery* 1998;123:539–544.

51. Ivarsson ML, Holmdahl L, Eriksson E, et al. Expression and kinetics of fibrinolytic components in plasma and peritoneum during abdominal surgery. *Fibrinolysis Proteolysis* 1998; 12:61–67.

52. Ivarsson ML, Falk P, Holmdahl L. Response of visceral peritoneum to abdominal sugery. *Br J Surg* 2001;88:148–151.

53. Reijnen MM, van Goor H, Falk P, et al. Sodium hyaluronate increases the fibrinolytic response of human peritoneal mesothelial cells exposed to tumor necrosis factor alpha. *Arch Surg* 2001;136:291–295.

54. Aruffo A, Stamenkovic I, Melnick M, et al. CD44 is the principal cell surface receptor for hyaluronate. *Cell* 1990; 61:1303–1313.

55. Culty M, Miyake K, Kincade PW, et al. The hyaluronate receptor is a member of the CD44 (H-CAM) family of cell surface glycoproteins. *J Cell Biol* 1990;111(6 Pt 1):2765–2774.

56. Yung S, Thomas GJ, Davies M. Induction of hyaluronan metabolism after mechanical injury of human peritoneal mesothelial cells in vitro. *Kidney Int* 2000;58:1953–1962.

57. Reijnen MM, Falk P, van Goor H, et al. The antiadhesive agent sodium hyaluronate increases the proliferation rate of human peritoneal mesothelial cells. *Fertil Steril* 2000;74:146–151.

58. Chen WY, Abatangelo G. Functions of hyaluronan in wound repair. *Wound Repair Regen* 1999;7:79–89.