Evaluation of sodium carboxymethylcellulose for prevention of experimentally induced abdominal adhesions in ponies

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SUMMARY

Twelve ponies were used to evaluate the reliability of an abdominal adhesion model and the efficacy of intraperitoneal infusion of sodium carboxymethylcellulose in preventing abdominal adhesions. A celiotomy was performed on each of the 12 ponies and the serosa of the distal portion of the jejunum was abraded with a dry gauze sponge at 5 locations. In addition to the serosal damage, a single 2-0 chromic gut suture was placed through the seromuscular layer of the jejunum in the center of the abraded area. After closure of the celiotomy, a 1% solution of sodium carboxymethylcellulose (7 ml/kg of body weight) was infused into the peritoneal cavity of 6 ponies. The other ponies served as untreated controls. All ponies were euthanatized 14 days after surgery.

All ponies in the control group had abdominal adhesions at the time of necropsy. Four of the 6 ponies in the treatment group were free of adhesions. There was a significant ($P < 0.0001$) difference in the total number of adhesions between the 2 groups.

Postoperative formation of peritoneal adhesions is a potential complication of abdominal surgery. Peritoneal adhesions form from fibrin deposition (fibrinous adhesions) produced in response to an insult to the peritoneum. Under normal circumstances, fibrin is lysed and absorbed but, in some cases, fibrin may remain and become invaded by fibroblasts, resulting in irreversible fibrous adhesions. Fibrous adhesions are more common in human beings, cattle, and horses than in cats and dogs, in which dissolution of major adhesions is common.[1] Adhesions are a clinical problem when they compress or anatomically distort the intestine. Adhesions also can form internal hernial rings or predispose to formation of volvulus.[2]

Numerous clinical trials and laboratory investigations have been devoted to the prevention of adhesions. High molecular weight solutions infused into the abdominal cavity of rats and rabbits have been used to prevent adhesion formation after surgical trauma.[3-7] Such agents are believed to provide a mechanical lubricating barrier between adjacent serosal surfaces, thereby preventing formation of adhesions.[3,4]

Sodium carboxymethylcellulose (SCMC) is a substituted polysaccharide that is prepared by reacting sodium monochloracetate with cellulose. Available food-grade forms may have a molecular weight as great as 350,000.[3,4] Solutions of SCMC have decreased the frequency of adhesion formation after abdominal surgery in rabbits and rats.[3-5] The purposes of the study reported here were to develop a reliable technique for inducing peritoneal adhesion formation in ponies and to determine whether SCMC infused into the peritoneal cavity after a serosal insult would prevent the formation of abdominal adhesions.

Materials and Methods

Ponies—Twelve clinically normal ponies with a mean age of 8.5 years (range, 1 to 22 years) were used. The ponies were dewormed by oral administration of ivermectin and vaccinated against tetanus, eastern and western encephalomyelitis, and influenza. Prior to the study, the ponies were maintained in a paddock, fed a 12% protein pelleted concentrate, and allowed free access to coastal Bermuda hay and water. Each pony was assigned to the control group (control) or the treatment group (treatment), and was housed in a 3.7 × 3.7-m box stall during the 2 weeks of the study.

Preparation of SCMC—A 1% solution of SCMC was prepared by boiling 200 ml of sterile water and adding 10 g of SCMC[a] powder while stirring. After the SCMC was in the solution, additional sterile water was added while stirring to bring the total volume to 1 L. The SCMC solution was then transferred into 500-ml glass bottles and autoclaved at 121 C for 20 minutes.

Adhesion model (control)—Six ponies (control ponies 1 to 6) were used to create a serosal adhesion model. Food was withheld from the ponies for 12 hours prior to surgery. Anesthesia was induced with xylazine hydrochloride (1.1 mg/kg of body weight, IV) followed by ketamine

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[a] Sodium carboxymethylcellulose (grade 7H3SF), Hercules Inc, Wilmington, Del.

hydrochloride (2.2 mg/kg of body weight, IV) and maintained with halothane in oxygen. After a ventral midline incision, the ileum was exteriorized and the most proximal end of the antimesenteric band was used as a reference point. From this point, a piece of suture material of known length was used to measure approximately 68 cm proximally along the jejunum. A dry gauze sponge was rubbed 100 times against the jejunal serosa at this point, causing an abraded area approximately 5 × 3 cm that was designated as A1. A single 2-0 chromic gut suture was then placed through the seromuscular layer of the jejunum in the center of the abraded area. The procedure was repeated to induce a total of 5 lesions at 68-cm intervals proximally on the jejunum.

In closing the abdomen, the peritoneum was not sutured, but linea alba was closed with No. 2 polyglycolic acid in a simple continuous pattern and the subcutaneous tissue was closed with 2-0 chromic gut in a simple continuous pattern. The skin was closed with No. 1 polyamide in a continuous horizontal mattress pattern. Immediately after recovery from anesthesia, the ponies were returned to their stalls and allowed free access to water and coastal Bermuda hay. Pelleted feed was added to their diet the morning after surgery. Neither antibacterial nor anti-inflammatory drugs were administered to any of the ponies during the experiment.

Treatment group—Prior to surgery, the 6 ponies assigned to the treatment group (treatment ponies 1 to 6) were maintained in the same manner as the control-group ponies. Induction of anesthesia and preparation of the treatment ponies for surgery were identical to the procedures described for the control ponies. A ventral midline celiotomy was performed and the procedure for traumatizing the jejunum was followed; however, before closure of the linea alba, a stab incision was made, using a No. 22 blade, through all layers of the abdominal wall 4 cm lateral to the initial incision. A 16-F Foley catheter was inserted into the peritoneal cavity through this incision. After closure of the abdominal incision, a sterile dose syringe was used to infuse sterile 1% SCMC solution (7 ml/kg of body weight) through the Foley catheter. The catheter was removed from the abdomen and the stab incision was closed with a single nonabsorbable suture. Postoperative management of ponies in the treatment group was the same as that for ponies in the control group.

Clinical assessment—Each pony was monitored daily for signs of pain, incisional swelling or drainage, food consumption, pulse and respiratory rates, and rectal temperature.

Clinicopathologic evaluation—On days 0, 1, 3, and 5, venous blood specimens were collected from the 6 ponies in the treatment group for hematologic and biochemical analysis. White blood cell counts were performed by use of a particle counter and differential WBC counts were made from blood smears. Fibrinogen concentration was determined by calculating the difference between total protein values of serum and plasma.

Values for total bilirubin, γ-glutamyltransferase (GGT), aspartate transaminase (AST), creatine kinase (CK), creatinine, glucose, BUN, total protein (TP), albumin, globulin, calcium, phosphorus,[b,c] and L-iditol dehydrogenase (ID) were determined. Sodium, potassium, chloride, and carbon dioxide determinations were performed, using ion-selective electrodes,[d] and anion gap was calculated. Serum osmolality was performed on a vapor pressure osmometer.[e]

Necropsy—Ponies in both groups were euthanatized with a concentrated pentobarbital sodium solution 14 days after surgery. The abdominal incision, peritoneal cavity, and all abdominal organs were evaluated for adhesions and any other abnormalities that could be related to intestinal abrasion or the SCMC, as well as adhesions unassociated with the abraded areas. Adhesions were designated as fibrinous if they could easily be pulled apart or fibrous if they could not be pulled apart without tearing serosa.

Statistical analysis—A chi-square test was used to compare the total number of adhesions in ponies from the control group with the number of adhesions in ponies from the treatment group. In addition, the mean, SEM, and minimal and maximal values were determined for the results of hematologic and biochemical tests for the treatment group. A statistical software system was used for all statistical analyses.[8]

Results

All ponies recovered from anesthesia without incident. Various degrees of incisional swelling developed in ponies of each group, but there was no drainage to indicate infection. With the exception of treatment pony 5, all ponies were active and ate well after surgery. Treatment pony 5 became depressed, febrile (rectal temperature, 39.1 C), and anorectic the day after surgery, but its food intake improved and pyrexia resolved without treatment by day 3. Four other ponies (control ponies 2, 3, 4, and treatment pony 4) had high rectal temperatures (38.7 C to 38.9 C) during the postoperative period, but were otherwise clinically normal.

Presurgical hematologic and biochemical values for the ponies in the treatment group were similar to values established as normal for our laboratory. The mean value of ID peaked 24 hours after surgery and was still higher than normal on day 5. The mean value of glucose was high 24 hours after surgery and had returned to normal by day 3. The mean value of calcium was low 24 hours after surgery and had returned to the normal range by day 3. On day 3, the mean value of fibrinogen was higher than normal and had not returned to normal values by day 5.

At necropsy, all control-group ponies and 2 ponies in the treatment group had abdominal adhesions. The number of adhesions at areas of serosal damage and additional adhesions not associated with the abraded areas were significantly ($P < 0.0001$) different between the 2 groups. All adhesions found at necropsy were fibrous adhesions. Signs of peritonitis, such as diffusely inflamed serosa or an abundant amount of peritoneal fluid, were not seen in ponies of either group.

[b] Cobas Mira Chemistry Analyzer, Roche *Diagnostic Systems, Nultey, NJ.*
[c] Sorbitol dehydrogenase, Sigma Chemical Co, St Louis, Mo.
[d] Beckman E4A Electrode Analyzer, Beckman Instruments Inc, Brea, Calif.
[e] Model 5500 Vapor Pressure Osmometer, Wiscoe, Logan, Utah.

Discussion

All ponies in the control group had at least 1 adhesion, indicating the predictability of the adhesion model. This adhesion model was chosen because serosal trauma has been established as a reliable means of adhesion formation in horses, rats, and rabbits.[9-17] In addition to serosal trauma, a chromic gut suture was placed in the abraded areas because sutures act as foreign bodies and can cause tissue ischemia, thereby increasing the probability of development of adhesions.[13,18–22]

Ponies that were given SCMC had significantly ($P < 0.0001$) fewer abdominal adhesions than control ponies. Sodium carboxymethylcellulose was chosen as an adhesion preventive because of its ability to prevent adhesion formation in rats and rabbits.[3-5] Sodium carboxymethylcellulose is highly viscous. It may serve as a lubricant and may mimic the hydrofloatation effect of dextran.[7] In studies in rats and rabbits, SCMC was safer and more efficacious than dextran[3-5,23] in preventing adhesions.

Formation of adhesions begins during the inflammatory stage of healing, 24 to 48 hours after injury, and the adhesions usually are well formed by 5 to 7 days after injury.[10,24,25] Intraperitoneal structures will not permanently heal to each other unless they are held in close contact during this period.[24] Sodium carboxymethylcellulose may act by keeping segments of intestine from remaining in contact with each other during this healing phase. The volume of SCMC used was extrapolated from a study performed in rabbits.[5] A larger volume of SCMC may further decrease the number of postoperative adhesions. Three control ponies had adhesions of the cecum to the ventral midline incision, whereas none of the ponies given SCMC had this type of adhesion. The SCMC may have pooled at the most dependent portion of the abdomen, thus preventing adhesions to the celiotomy incision. All adhesions in ponies from the group given SCMC involved only adherence of omentum to 1 of the abraded areas.

A major consideration for choosing an agent to prevent adhesions is the possibility of deleterious effects. In dermatologic and toxicologic studies in other species, SCMC had no evidence of toxicity.[26] In this trial, mean ID activity peaked on day 1, and remained higher than normal through the fifth day. Similar ID activity has been reported in horses anesthetized with halothane and does not necessarily reflect a toxic effect of SCMC.[27] Also, a horse with transient gastrointestinal tract disease may develop an increase in ID activity[28]; therefore, trauma to the intestine may have initiated the increase in ID activity.

Mean glucose values were high on day 1 but had returned to normal by day 3. This likely was a result of abdominal pain induced by surgery. Modest increases in blood glucose values result from release of endogenous epinephrine or corticosteroid in response to stress and can be expected with abdominal pain, regardless of the cause.[28] The mean value of fibrinogen was high on day 3 and remained high through day 5. This increase was expected as a normal response to inflammation. The mean calcium values were low on day 1, but were normal by day 3. We have no explanation for this finding.

Evaluation of the treatment ponies, including clinical appearance and hematologic and biochemical values, did not indicate any obvious deleterious effects from intraperitoneal infusion of 1% SCMC. Because little is known about the extent and manner in which SCMC is excreted,[5] further investigation is warranted before SCMC can be recommended for routine use in horses.

The most common cause of small intestinal obstruction in human beings is abdominal adhesions caused by surgical trauma.[9,19,29] This also could be true in other species. The goal of the surgeon is to stop the undesirable formation of fibrous adhesions without suppressing the mesothelial regeneration that is necessary for covering the damaged area of serosa. Whether SCMC can prevent adhesions that form as a result of tissue ischemia has not been determined. Adhesions that form in response to ischemia act as vascular grafts from healthy tissue into devitalized tissue and, in some cases, may be lifesaving.[13,24] Sodium carboxymethylcellulose may be contraindicated when used to prevent adhesions that could form as a result of a vascular insult, such as a volvulus of the small intestine.

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