Meta-Analysis of the Effects of Adhesion Barriers on Adhesion Formation in the Horse

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Objective: To determine the efficacy of adhesion barriers in horses using quantitative statistical analysis.

Study Design: Meta-analytical review.

Methods: A search using PubMed/MEDLINE and Google Scholar was performed, followed by secondary searches of veterinary trade journals, bibliographies of relevant articles, manufacturer websites, and technical reference guides. Randomized experimental trials in healthy horses were considered that included both a treatment and control group. The endpoint required was euthanasia or laparoscopy to identify adhesion formation. A meta-analysis was performed using a random effects model, with the effect size calculated as an odds ratio (OR) with 95% confidence intervals (CI). Statistical significance was set at $P<.05$.

Results: Out of 354 peer reviewed publications that met the search criteria, a total of 9 relevant studies were identified and investigated the use of sodium carboxymethylcellulose (CMC) solutions, sodium hyaluronate/carboxymethylcellulose (HA/CMC) membranes, hyaluronate (HA), and fucoidan solutions. The odds of adhesions in horses treated with an adhesion barrier were significantly lower than untreated controls (OR=0.102; 95% CI [0.041, 0.254]; $P<.001$). When analyzed as subsets for each type of barrier, horses treated with HA/CMC membranes and CMC solutions had significant OR for fewer adhesions (OR=0.061; 95% CI [0.013, 0.292]; OR=0.119; 95% CI [0.034, 0.415], respectively; $P<.001$).

Conclusion: The meta-analysis demonstrated adhesion barriers provide a positive effect on the odds of adhesion formation. These results are tempered by the limitations of the study, including the small sample size and a bias towards publication of studies with only positive findings.

Intra-abdominal adhesions are anomalous bands or sheets of tissue that can form on serosal surfaces within the peritoneal cavity secondary to bowel ischemia, mechanical trauma, peritonitis, hemorrhage, or a genetic predisposition.[1] Adhesions can cause significant clinical morbidity in horses, including bowel obstruction, chronic abdominal pain, and inadvertent organ injury during repeat laparotomy.[2–4] The incidence of pathologic adhesions has been reported to be up to 32% in horses subjected to repeat laparotomy for abdominal disease.[4] However, the true incidence of adhesions may be higher, since adhesions can only be diagnosed by visualization during surgery or at necropsy.

While surgical adhesiolysis is possible in select cases, this procedure has all of the drawbacks associated with abdominal surgery, including the additional risks of adhesion reformation and the possibility that the lesion may not be resectable.[5,6] Therefore, therapy for adhesions is currently focused on prevention, which can be divided into three categories: good surgical technique, pharmacologic modulation of coagulation pathways and inflammation, and physical adhesion barriers, including gels, solutions, and solid membranes.[7] Adhesion barriers act by providing physical separation between serosal surfaces and by preventing fibrinous deposits from linking the surfaces by a fibrin adhesion. The veterinary literature reports that these barriers reduce the frequency of adhesions in clinical cases; however, these are often observational reports of patient survival, rather than evidence of efficacy.[8,9] There are experimental studies that have tested these materials in horses and while some have shown a reduction in the frequency of adhesions using adhesion barriers,[10–15] others have shown no effect in controlled, randomized trials.[16–20] Therefore, the goal of this study was to perform a meta-analytic review of adhesion barriers tested experimentally in horses and to identify the effect of these agents on adhesion formation.

Reviews in veterinary medicine have traditionally followed a narrative style, which can introduce bias through the authors' study selection and a subjective interpretation of the article.[21] A second flaw of review papers is the use of vote counting as the statistical means to summarize the effect. In the vote counting process the significant and insignificant outcomes are numerically tallied and compared to determine the

magnitude of interest. The results of a vote count are influenced by the magnitude of the response, the sample size, and the variability in the data. Issues with vote counting include incorrect conclusions because of sample size and a biased estimate because of low statistical power.[22,23] In veterinary medicine, vote counting often results in the failure to reject the null hypothesis, because of both small sample sizes and small overall effects.[21]

Meta-analysis is a statistical, quantitative method designed to compare and synthesize the diverse results of multiple studies.[24] This type of statistical summary recognizes the heterogeneous nature of the studies included and weights each study based on sample size. Questions that can be answered using meta-analysis include the magnitude of effect and the difference of the effect from the null hypothesis or zero.[25] By transforming the results or study statistics of each paper into a common factor, called an effect size, this allows for direct comparison of studies, as well as comparison of predefined groups within the study and experimental manipulations. Meta-analysis is particularly helpful in veterinary studies, where effect size and sample size are often restricted, to reduce type 2 statistical errors that can lead the researcher to fail to reject a false null hypothesis.

The purpose of this study was to provide a systematic meta-analytic assessment of the overall efficacy of adhesion barrier methods in the prevention of adhesions. The primary objective was to determine the success of each class of barrier in prevention of adhesions in the whole animal (horse) using controlled, experimental studies that have assessed adhesion formation in models of serosal irritation and inflammation. The secondary objectives were to evaluate the effect of these barriers on the number of adhesions per horse, as well as any effect of adjunct therapies, specifically antibiotics and anti-inflammatory medications, on outcome measures. We hypothesized that barrier methods would reduce the frequency and severity of adhesions in the horse and that the concurrent use of antibiotics and anti-inflammatory medications would enhance the effects of the adhesion barriers and further reduce the odds of adhesion formation in horses treated with adhesion barriers.

MATERIALS AND METHODS

Literature Search

A comprehensive literature search was carried out utilizing PubMed/MEDLINE from January 1946 to April 2014. The results were scrutinized for additional articles using PubMed's *Suggested Related Citations* lists. A second search was performed with Google Scholar for papers published up to April 1, 2014. No language or date restrictions were applied. Key words used in the database search included "equine" or "horse," and "adhesion* and abdominal," or "adhesion* and intraabdominal," or "adhesion* and peritoneal," or "adhesion* and intraperitoneal."

Secondary searches were performed to identify specific studies using prophylactic agents that provide a physical barrier to the formation of intra-abdominal adhesions. These included searches that combined "equine" or "horse" and "adhesion*" with "carboxymethylcellulose," "hyaluronan," "hyaluronate," "hyaluronic acid," "Seprafilm" (Genzyme Biosurgery, Framingham, MA), "fucoidan," "Peridan" (Bioniche Animal Health, Athens, GA), "Interceed" (Ethicon Endo-Surgery, Inc, Cincinnati, OH), "polytetrafluoroethylene," "icodextran," or "Adept" (Baxter Healthcare Corp, Deerfield, IL). Finally, the search engines of specific veterinary trade journals (*Veterinary Surgery, Journal of the American Veterinary Medical Association, American Journal of Veterinary Research, Journal of Veterinary Internal Medicine, and Equine Veterinary Journal*) were mined with the key words to locate studies published only as abstracts or poster presentations.

Additional papers were identified with a manual search of the bibliographies of relevant articles identified in the initial search. Published review articles on abdominal adhesions in horses identified from these queries were also searched for related publications.[1,26–29] Finally, the manufacturers of commercial prophylactic agents mentioned above were identified and relevant publications were obtained from technical reference guides or manufacturer's websites.

Paper Selection

Identified articles were screened using the title and abstract to identify those that met the inclusion criteria. Criteria for inclusion in the meta-analysis included the following: (1) the study was a prospective, randomized, experimental trial, with control and treated groups; (2) the surgical procedure performed involved experimental induction of adhesions through a published method for serosal inflammation (abrasion, suture implantation, anastomosis, ischemia); (3) the endpoint was euthanasia or laparoscopic exploratory to identify adhesions, and (4) the experiment involved the equine species. The studies included were required to compare either no intervention or a placebo against a single selected adhesion barrier. Signalment of the horse (age, breed, sex) was not restricted. The quality of the studies were not rated and all relevant studies were included that fit the criteria.

General reviews, retrospective and prospective clinical trials, cohort studies, and observational studies were not included in the meta-analysis, because of the lack of one or more of the previous inclusion criteria (direct observation of adhesions, lack of a control group, adhesion barriers were not tested). Abstracts were included if it was possible to identify the outcome measures for the study. If the outcome measures were not defined, the authors of the papers or abstracts were contacted to obtain unpublished data. Studies were excluded from meta-analysis if it was impossible to extract or calculate the appropriate data from the results or if the raw data was not available for re-analysis.

Outcomes Assessed

The primary outcome measure for this study was the observation of adhesions in the abdomen of the horse at necropsy or by laparoscopy. Papers were included only if the adhesions

were clearly identified and enumerated for each horse. In addition, subgroup analyses were performed to identify the effect of adjunct therapies, specifically non-steroidal anti-inflammatory medications and antibiotics, on adhesion formation.

Data and Statistical Analysis

Identification of papers and extraction of data was performed by two researchers (AM, JK). Data collected included the author(s), journal, title of the work, year of publication, signalment of horses involved (breed, age, weight, sex), number of subjects in the treated and control groups, type of adhesion model used, and timing of assessment (necropsy or second-look laparoscopy related to date of index surgery). Interventions noted included the prophylactic agent used, concentrations of barrier solutions, site(s) of application, and adjunct agents used [antibiotic(s), anti-inflammatory medication(s)]. Outcome measures included frequency of adhesions at the level of the horse in the experimental and control groups (a dichotomous response), the number of sites affected, and the type of adhesion(s).

Data analysis was performed (CMA software, Comprehensive Meta-analysis, Biostat, Inc, Engelwood, NJ) to analyze, interpret, and synthesize the data. A meta-analysis was performed for trials that reported complete data for the predefined outcomes, assuming a random effects model when there was evidence of statistical heterogeneity. For dichotomous data, including the presence or absence of adhesions, the impact of the intervention was expressed as an odds ratio (OR) with 95% confidence intervals (CI).

The OR was calculated using the CMA software where data was entered in a 2 × 2 table format, such that A = treated with development of adhesions, B = treated without development of adhesions, C = control with development of adhesions, and D = control without development of adhesions.[24] The OR were converted to log scale by the CMA program to maintain symmetry in the analysis and for all comparisons. The log scale was then converted back to the original metric by the CMA program for the summary statistics. For analysis of the number of adhesions per site per horse, the counts were converted to an OR with 95% CI to provide a standardized effect size. Heterogeneity, which is the degree of dissimilarity in the results of the selected studies, was assessed using the χ^2 test (where $P<.1$ was considered statistically significant) and the I^2 statistic (where $I^2 \geq 50\%$ represents substantial heterogeneity between studies). Heterogeneity was also tested by visual inspection of a forest plot for lack of overlap of the CI. $P<.05$ was considered statistically significant.

Bias in meta-analysis can occur if the studies included in the meta-analysis are not representative of the studies conducted.[30] One explanation for how studies introduce bias is that there is innate bias in the studies selected for publication, where studies with a significant *P*-value are more likely to be selected for publication. A second explanation is that there is bias in the retrieval of studies for the meta-analysis because of access by the author. To explore for potential publication bias, a funnel plot of standard error plotted against the log OR of primary outcome for the studies included in the meta-analysis was performed. The larger, more powerful studies will lie towards the top of the plot, and weaker, less influential studies will disperse towards the bottom. In the absence of bias, 95% of studies would be expected to lie within the triangular region of the graph.

RESULTS

Description of Included Studies

The described search strategy identified a total of 354 peer reviewed publications. The abstracts and titles of these selected studies were then evaluated to identify papers that met the selection criteria, resulting in the exclusion of 346 publications. A total of 5 additional papers, including 2 abstracts and a Master's thesis, were identified from manufacturer's websites, bibliographies, review articles, and veterinary journal search engines. Studies removed included clinical trials, review articles, experiments performed in other species, those that did not evaluate adhesion barriers, and studies without the specified endpoints. Papers were also excluded that did not use an established experimental surgical model of adhesion formation.

After applying the exclusion criteria, a total of 13 relevant sources were identified, evaluating 149 horses, which were included in the qualitative assessment (Table 1). Dates of publication ranged from 1989 to 2012. An additional 4 papers were excluded from the quantitative meta-analysis because of a lack of clear data for the number and type of adhesions noted in each horse.[12,13,16,31] In the case of the publication by Moll, there was insufficient data available for comparison from the publication.[13] A Master's thesis identified as the source of the data published in the paper was analyzed as an alternative and used to collect the pertinent data for the meta-analysis.[32] For the final analysis, a total of 9 papers contained the necessary data for the primary outcome, the odds of development of adhesions in the horse. These studies investigated the use of sodium carboxymethylcellulose (CMC) solutions, sodium hyaluronate/carboxymethylcellulose (HA/CMC) membranes, sodium hyaluronate (HA) solutions, and fucoidan solutions.

The types of adhesion models used to induce adhesions, as well as peri-operative therapies, varied widely in these studies. Some studies used jejunal anastomoses only,[10,18,19] while a single study by Moll used serosal abrasions with a dry gauze in conjunction with suture placed in the abraded area to stimulate reaction to a foreign body.[32] Most studies used a combination of a number of distinct abrasion sites, with one or more jejunal anastomoses to simulate bowel resections or enterotomies.[11,14,15,20] One report by Lopes used a model of ischemia, subsequent to temporary occlusion of the jejunal arcades.[17] Two of the papers tested 2 separate adhesion barriers against the same control group, and the treated groups vs. the single control for each paper were treated as separate experiments for analysis purposes.[10,20]

Table 1 Relevant publications included in the qualitative assessment for meta-analysis of randomized experimental trials evaluating the effects of adhesion barriers on intra-abdominal adhesion formation in horses

Study and year	Number of horses	Number and type of adhesion model	Adhesion barrier tested	Control	Time until re-evaluation*	Antibiotics and anti-inflammatory medications used; duration
Eggleston et al[19] (2001)[†]	6 treated; 6 control	Single jejunal anastomosis	HA/CMC membrane	No treatment	21 days	Penicillin, gentamicin, flunixin meglumine; 48 hours
Eggleston et al[20] (2004)	6 treated; 6 control	Single jejunal anastomosis; 2 abrasion sites with serosal sutures	0.4% wt/wt HA; 1% wt/wt CMC	No treatment	10 days	Penicillin, gentamicin, flunixin meglumine; 48 hours
Hay et al[14] (2001)	6 treated; 6 control	2 jejunal anastomoses; 2 abrasion sites with serosal sutures	1% wt/wt CMC	0.9% saline	10 days	Penicillin, gentamicin, flunixin meglumine; 48 hours
Lopes et al[17] (1998)	9 treated; 9 control	4 horses-one ischemic section and 5 jejunal abrasion sites with serosal sutures; 14 horses-four ischemic sections and 5 jejunal abrasion sites with serosal sutures	1% wt/wt CMC	No treatment	14 days	Penicillin, gentamicin; 48 hours
Moll et al[13,32] (1989 and 1991)	6 treated; 6 control	5 jejunal abrasion sites with serosal sutures	1% wt/wt CMC	No treatment	14 days	None
Morello et al[18] (2012)	6 treated; 6 control	2 jejunal anastomoses	2.5 g fucoidan in 5L LRS	LRS solution	10 days	Penicillin, 24 hours; gentamicin, 48 hours; flunixin meglumine, 72 hours
Mueller et al[15] (1998)	6 treated; 6 control	2 jejunal anastomoses; 2 abrasion sites with serosal sutures	HA/CMC membrane	No treatment	10 days	Penicillin, gentamicin, flunixin meglumine; 48 hours
Mueller et al[10] (2000)	6 treated; 6 control	Single jejunal anastomosis	HA/CMC membrane; 1% wt/wt CMC	No treatment	10 days	Penicillin, gentamicin, flunixin meglumine; 48 hours
Mueller et al[11] (2000)	6 treated; 6 control	2 jejunal anastomoses; 2 abrasion sites with serosal sutures	HA/CMC membrane	No treatment	10 days	Penicillin, gentamicin, flunixin meglumine; 48 hours
Murphy et al[12] (2002)	5 treated, 5 control	Typhlotomy; 5–6 abrasion sites with serosal sutures	1% wt/wt CMC	No treatment	10 days	None
Sullins et al[16] (2004)	4 treated CMC; 6 control (no treatment); 4 untreated (antibiotics and anti-inflammatories)	Ischemia-one 24 cm section	3% wt/wt CMC	No treatment	10 days	Penicillin, gentamicin, flunixin meglumine; 72 hours as the sole treatment in one group of 4 horses
Yamout et al[31] (2007)	6 treated; 6 control	4 jejunal abrasions	600 mL 0.03% wt/v fucoidan	600 mL LRS	10 days	Data lacking

*All studies used necropsy to assess adhesion formation, except for Yamout et al, where laparoscopy was used.
[†]Meta-analysis includes only a control group with a similar suture technique (single layer inverting pattern) to the treated group. A second treatment group with a double inverting technique was not included in the analysis.
CMC, sodium carboxymethylcellulose solution; HA, sodium hyaluronate; HA/CMC, sodium hyaluronate/carboxymethylcellulose; LRS, lactated Ringer's solution.

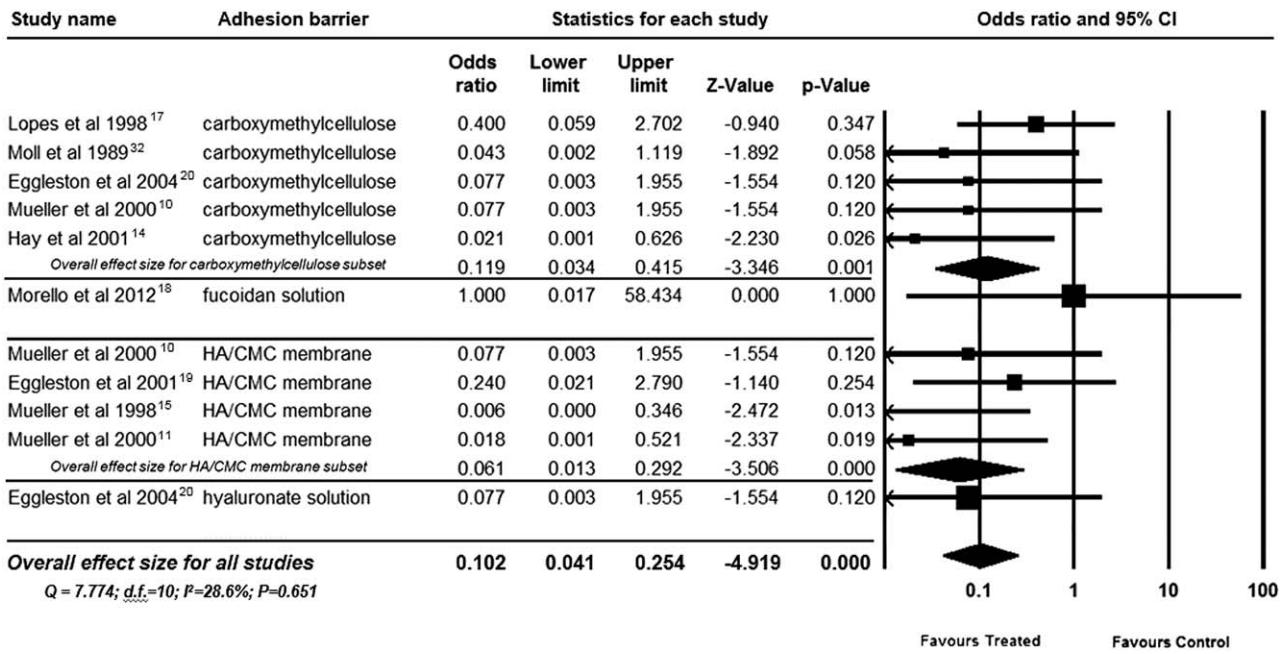

Figure 1 Meta-analysis comparing the odds of adhesions for experimental horses treated with adhesion barriers for all papers. An OR=1 indicates no difference between treatment and control, whereas an OR<1 indicates the treatment reduced the frequency of adhesions. Conversely, an OR>1 would indicate a negative effect of the treatment regarding adhesion formation. Confidence intervals (95% CI) that overlap suggest a lack of association between the treatment and the outcome. $P<.05$ indicates significant differences between treatment and control.

Of the 9 studies included for quantitative review, 8 papers administered peri-operative antibiotics and anti-inflammatory medications. In the study by Lopes, the horses were provided antibiotic coverage, but they were not administered anti-inflammatory medications.[17] The study by Moll did not administer either class of medication.[32]

Outcomes

A total of 9 publications were suitable for meta-analysis; however, 2 contained assessments of 2 separate barriers, resulting in 11 comparisons (Fig 1). Using a random effects model for meta-analysis, the frequency of adhesions in horses treated with an adhesion barrier was significantly lower than the untreated control group (OR=0.102; 95% CI [0.041, 0.254]; $P<.001$). A subset analysis was performed to determine the odds of adhesion formation for each type of adhesion barrier used in the studies included in the meta-analysis. Compared to controls, both HA/CMC membranes (OR=0.061; 95% CI [0.013, 0.292]; $P<.001$) and CMC solutions (OR=0.119; 95% CI [0.034, 0.415]; $P=.001$) had lower OR for adhesion formation. Unfortunately, there was only 1 representative publication in the meta-analysis for both fucoidan solution and HA solution. The study by Eggleston evaluating an HA solution had an OR=0.077 (95% CI [0.003, 1.955]; $P=.120$), suggesting no effect.[20] The OR for adhesions in horses treated with fucoidan solution in the paper by Morello was also not significantly different from the control groups (OR 1.00; 95% CI [0.017, 58.434]; $P=1.00$).[18]

A total of 7 of the comparisons in this meta-analysis administered systemic antibiotics (penicillin, gentamicin) and non-steroidal anti-inflammatory medications (flunixin meglumine) for 48 hours peri-operatively.[10,11,14,15,19,20] Morello treated with antibiotics for 24 hours and flunixin meglumine for 72 hours.[18] A single study by Lopes did not use perioperative anti-inflammatories, but did administer 24 hours of antibiotics, and separate study by Moll did not administer either antibiotics or anti-inflammatory medications.[17,32] When these 2 studies were excluded from the analysis, the revised OR=0.072 for studies that administered these drugs (95% CI [0.024, 0.215]; $P<.001$). When examined as a subset, the OR for Lopes and Moll was not significantly different from the controls (OR=0.226; 95% CI [0.043, 1.176]; $P=.077$).[17,32]

To evaluate the effect of the adhesion barrier on severity of adhesions based on the number of adhesions per horse, the average number of adhesions formed at the iatrogenic sites of damage was compared between treated and control groups. Only 8 studies contained relevant data for meta-analysis (Fig 2).[11,14,15,17–20,32] There were 4 papers evaluating CMC solutions, 3 papers evaluating HA/CMC membranes, and 1 that assessed a fucoidan solution. The paper by Eggleston, which evaluated a CMC solution also assessed an HA solution, and was included as 2 separate comparisons.[20] Using an OR as the effect size, the meta-analysis noted a significantly lower frequency of adhesions for horses treated with adhesion barriers than the controls (OR=0.164; 95% CI [0.097, 0.254]; $P<.001$). When analyzed separately by type of adhesion barrier, the OR for all barrier methods except fucoidan solution were lower than the controls.

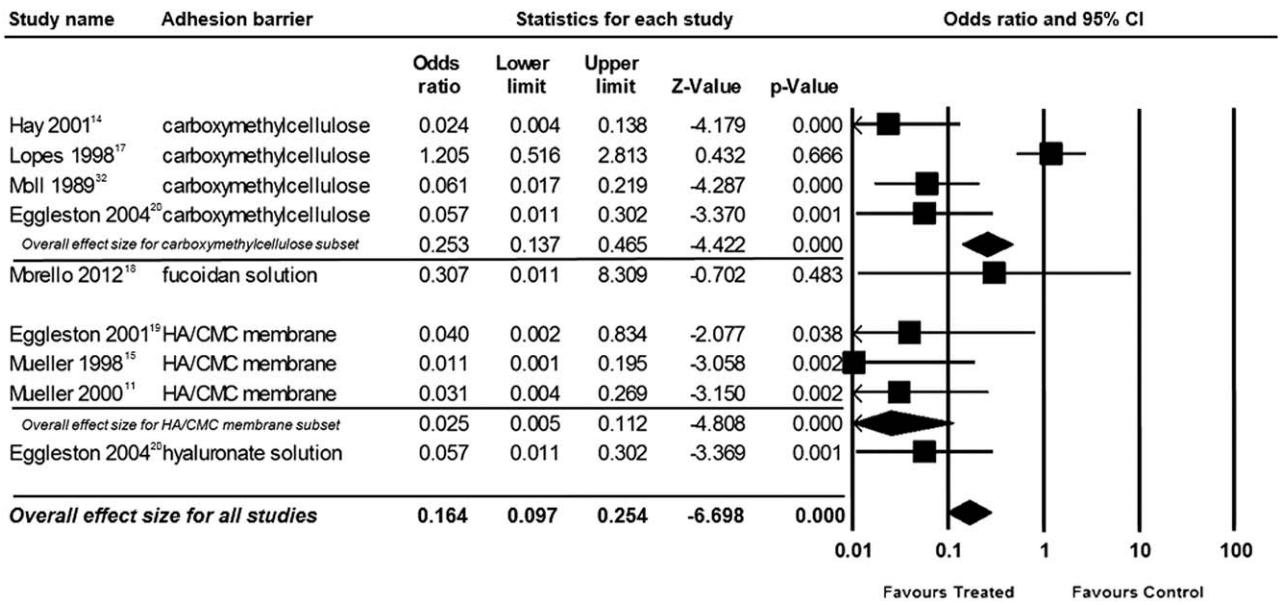

Figure 2 Meta-analysis comparing the odds of a positive effect on the frequency of adhesions for experimental horses treated with adhesion barriers with subset analysis for each type of adhesion barrier. An OR=1 indicates no difference between treatment and control, whereas an OR<1 indicates the treatment reduced the frequency of adhesions. Conversely, an OR>1 would indicate a negative effect of the treatment regarding adhesion formation. Confidence intervals (95% CI) that overlap suggest a lack of association between the treatment and the outcome. $P<.05$ indicates significant differences between treatment and control. The subset treated with adhesion barriers showed a significantly lower frequency of adhesion formation than untreated controls. When analyzed separately by type of adhesion barrier, horses treated with carboxymethylcellulose solutions, hyaluronate/carboxymethylcellulose membranes (HA/CMC), and hyaluronate solutions demonstrated a significantly lower odds ratio than controls.

Publication Bias

A funnel plot of the 9 studies in the meta-analysis reporting the primary outcome for adhesion formation was diagrammed to assess publication bias. This graph is a scatter plot of the treatment effects as a log OR from the individual studies plotted on the horizontal axis against the standard error. All studies were within the 95% CI, implying a lack of publication bias. However, there are more studies that lie to the left of midline on the plot, indicating the data collected had a trend towards publications reporting a significant positive effect for the adhesion barriers tested. Heterogeneity was tested by evaluation of the forest plot, which noted overlap of the CI of all studies. Computation of the χ^2 test and I^2 were not significant, with a conservative type I error of 10% ($Q=7.774$; $df=10$; $I^2=28.6\%$; $P=.651$), supporting the evidence from the forest plot of a lack of heterogeneity in the studies evaluated.

DISCUSSION

In this meta-analysis of the available literature, adhesion barriers demonstrated an ability to reduce the odds of adhesion formation in experimental, randomized, controlled studies in the horse. Treated horses were 10 times less likely to develop adhesions than horses not treated with adhesion barriers. While the overall effect size of the meta-analysis was significant, it was interesting to note that the 95% CI for 8 of the 11 comparisons showed no significant difference from the controls. By combining the horses from the individual studies into a single effect size, the power of the analysis was improved, which narrowed the CI and may provide a better characterization of the true effect of the adhesion barriers on frequency of adhesions.[33] While the horses treated in these studies were experimental animals free of disease, the pooled effect size establishes a reference for the effect of these adhesion barriers that may be tested in future studies.

One critique of this meta-analysis is the small size of the comparison groups in the papers included in quantitative analysis. Small samples sizes are often criticized because of increased heterogeneity, lower quality methodology, and a trend towards reporting only larger or more beneficial treatment effects.[34] Safeguards against small study effects include identification of a lack of bias through a symmetrical funnel plot and re-analysis based on allocation by sample size. The studies included in this meta-analysis of adhesion barriers did trend towards a positive treatment effect; however, the funnel plot remained symmetrical, because of an even split between papers that identified a positive response and those that showed no benefit of treatment with an adhesion barrier. The selection criteria also included only experimental trials, which reduced bias caused by poor quality experimental methodology, such as lack of randomization. However, a meta-analysis of large, randomized clinical trials would provide an improved estimate of the true treatment effect.[34,35]

A subset analysis showed both HA/CMC membranes and CMC solutions reduced the odds of adhesion formation in treated horses. The meta-analysis was able to improve the statistical power of the studies included and provide a meaningful direction for further clinical investigations of adhesion barriers. It was not possible to further assess the effects of both HA and fucoidan solutions on adhesion formation, because each group only had one study available for analysis. Although the OR for HA solution was <1, its CI did not reach statistical significance.[20] The single fucoidan study included in this meta-analysis also showed no difference in adhesion formation between treated and controls.[18] An explanation for this finding could be that the resection model for adhesions in this study was not severe enough to induce adhesions in the horses, which minimized the effect of the adhesion barrier in this study. A more recent abstract evaluating fucoidan in pony foals showed a significant different in adhesion formation using an abrasion model for adhesions, with a difference in means of 4.0 (95% CI [1.7914, 6.2086], P=.01).[31] Unfortunately, specific data were not available from this abstract to include in our meta-analysis.

Both anti-inflammatory medications and prophylactic antibiotic therapy have been reported to reduce adhesion formation when administered peri-operatively in horses and other species.[16,36–38] These medications could have confounded the effects of the adhesion barriers tested, therefore studies that used these medications were removed and the groups reanalyzed as separate subsets. While the studies that treated horses with antibiotics and anti-inflammatory medications still showed a similar effect of the barriers on the odds of adhesion formation, the OR for the 2 studies that did not administer these drugs showed no difference between treated horses and the controls.[17,32] This could indicate that the adhesion barriers were not effective as a single preventative strategy or that the adhesion barriers had a negative effect that was offset by the anti-inflammatory medications or antibiotics. However, the small size of the studies, as well as the fact there were only 2 studies in this subset analysis, may have contributed to the lack of effect. Further investigation is necessary to determine the interaction of these medications and adhesion barriers on adhesion formation in the horse before making any conclusions from our meta-analysis. While the HA/CMC membrane showed a significant positive effect on the odds of adhesion formation, caution should be used in extrapolating the use of this barrier to clinical patients, based on evidence that HA/CMC membranes are associated with significant perioperative complications in people. A recent meta-analysis noted that use of HA/CMC membranes may increase the risk of abdominal abscesses in people with inflammatory bowel disease and was related to an increased incidence of anastomotic leakage.[39] In addition, site-specific barriers may not prevent adhesions that can form on serosal surfaces remote from the primarily lesion.[16] Clinically, a solution used to coat all surfaces handled or exposed at surgery would be recommended to prevent this complication and further investigations into the HA and fucoidan solutions, as well as novel compounds such as chitosan dextran and alginate gel, should be pursued.[40,41]

CMC solutions may also have negative side effects in the horse. In a retrospective study by Fogle et al, it was observed that horses treated clinically with CMC solution had an increased incidence of post-operative ileus.[9] The authors postulated that a low grade peritonitis may have reduced intestinal motility, which has been reported to increase adhesion formation in experimental subjects.[12] However, no evidence of peritonitis has been reported in studies that experimentally evaluated CMC solutions in the horse.[10,12,14,16,17,20,32] CMC solutions may also be absorbed systemically, forming a precipitate in peripheral blood smears.[42] Although serum fibrinogen was also increased in horses administered CMC in this study, there was no correlation with CMC dosage.[42] The significance of this precipitate is currently unknown. Adverse reactions to CMC solutions reported in people include anaphylactic shock after steroid injections or after barium enemas that contain CMC.[43]

In the human literature, similar to veterinary publications, there are a limited number of studies that have investigated adhesion barriers and their efficacy for reducing adhesions. In 1 meta-analysis of 7 studies evaluating HA/CMC membranes and a 0.5% ferric hyaluronate gel, HA/CMC membranes were reported to significantly reduce the odds of adhesions in people (OR=0.15; 95% CI [0.05, 0.43]; P<.001).[44] A second meta-analysis that evaluated only an HA/CMC membrane also reported a significant reduction in the severity of adhesions formed (OR=0.23; 95% CI [0.09, 0.63]; P=.004).[39] Other barriers studied that have shown significant effects on adhesion formation include polytetrafluoroethylene sheets and oxidized regenerated cellulose.[45] While HA solutions have been investigated in horses, both the high cost and commercial availability of these protective solutions and other barrier substances used in human medicine may prevent clinical application in horses.[11]

A significant limitation of this meta-analysis is that the study was restricted to experimental, prospective, randomized controlled studies rather than clinical trials in horses. Studies that have identified the incidence of naturally occurring adhesions after treatment with adhesion barriers are lacking in the veterinary literature. The gold standard for diagnosing adhesions would be a second-look surgery, either laparoscopically or by laparotomy. However, it is difficult to convince owners to allow their horse to undergo such an invasive procedure. In addition, the complications of adhesions may take years to occur and patients may be lost to follow-up. Because of the lack of evidence, a meta-analysis assessing the efficacy of adhesion barriers in clinical cases may not be possible, therefore our study may serve as a surrogate to provide for evidence-based surgical decisions.

Based on the current available evidence, both the HA/CMC membrane and a 1% CMC solution provide a significant benefit in reducing the odds of intra-abdominal adhesions in experimental models in normal horses. While the HA/CMC membrane may have shown an effect on adhesion formation, CMC solutions have the advantage of protecting the abdominal surfaces in general, rather than specific sites. No valid conclusions could be drawn regarding adhesion prevention using HA and fucoidan solutions individually,

because of the lack of sufficient data. Additional studies of these adhesion barriers are warranted in clinical cases or in models of disease that more closely mimic the systemic effects that cause adhesions.

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DISCLOSURE

The authors declare no conflicts of interest related to this report.

REFERENCES

1. Alonso JD, Alves AL, Watanabe MJ, et al: Peritoneal response to abdominal surgery: the role of equine abdominal adhesions and current prophylactic strategies. *Vet Med Int* 2014;2014: 279730.
2. Butson RJ, England GC, Blackmore CA: Omento-omental adhesion around the uterine horn as a cause of recurrent colic in a mare. *Vet Rec* 1996;139:571–572
3. Gorvy DA, Edwards GB, Proudman CJ: Intraabdominal adhesions in horses: a retrospective evaluation of repeat laparotomy in 99 horses with acute gastrointestinal disease. *Vet J* 2008;175:194–201
4. Norrie RD, Heistand DL: Chronic colic due to an omental adhesion in a mare. *J Am Vet Med Assoc* 1975;167:54–55
5. Bleyaert HF, Brown MP, Bonenclark G, et al: Laparoscopic adhesiolysis in a horse. *Vet Surg* 1997;26:492–496
6. Bouré L, Marcoux M, Lavoie JP, et al: Use of laparoscopic equipment to divide abdominal adhesions in a filly. *J Am Vet Med Assoc* 1998;212:845–847
7. Mueller POE: Prevention and treatment of postoperative intraabdominal adhesions in horses, in: White NA, Moore JN, Mair TS (eds): *Equine acute abdomen*. Jackson, WY, CRC Press, 2009, pp 119–129
8. Mueller PO, Hunt RJ, Allen D, et al: Intraperitoneal use of sodium carboxymethylcellulose in horses undergoing exploratory celiotomy. *Vet Surg* 1995;24:112–117
9. Fogle CA, Gerard MP, Elce YA, et al: Analysis of sodium carboxymethylcellulose administration and related factors associated with postoperative colic and survival in horses with small intestinal disease. *Vet Surg* 2008;37:558–563
10. 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
11. Mueller PO, Hay WP, Harmon B, et al: Evaluation of a bioresorbable hyaluronate-carboxymethylcellulose membrane for prevention of experimentally induced abdominal adhesions in horses. *Vet Surg* 2000;29:48–53
12. 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
13. Moll HD, Schumacher J, Wright JC, et al: Evaluation of sodium carboxymethylcellulose for prevention of experimentally induced abdominal adhesions in ponies. *Am J Vet Res* 1991;52:88–91
14. Hay WP, Mueller PO, Harmon B, et al: One percent sodium carboxymethylcellulose prevents experimentally induced abdominal adhesions in horses. *Vet Surg* 2001;30:223–227
15. Mueller POE, Hay WP, Harmon B, et al: Evaluation of a bioresorbable hyaluronate membrane for prevention of experimentally induced adhesions in horses. *Proc Am Assoc Equine Pract* 1998;44:260–262
16. Sullins KE, White NA, Lundin CS, et al: Prevention of ischaemia-induced small intestinal adhesions in foals. *Equine Vet J* 2004;36:370–375
17. Lopes, MAF, Dearo ACO, Paulo I, et al: Peritoneal adhesions in horses: prophylactic treatment with carboxymethylcellulose. *Ciencia Rural, Santa Maria* 1998;28:423–430
18. Morello S, Southwood LL, Engiles J, et al: Effect of intraperitoneal PERIDAN™ concentrate adhesion reduction device on clinical findings, infection, and tissue healing in an adult horse jejunojejunostomy model. *Vet Surg* 2012;41:568–581
19. Eggleston RB, Mueller POE, Quandt JE, et al: Use of a hyaluronate membrane for jejunal anastomosis in horses. *Am J Vet Res* 2001;62:1314–1319
20. Eggleston RB, Mueller PO, Parviainen AK, et al: Effect of carboxymethylcellulose and hyaluronate solutions on jejunal healing in horses. *Am J Vet Res* 2004;65:637–643
21. Gurevitch J, Curtis PS, Jones MH: Meta-analysis in ecology. *Adv Ecol Res* 2001;32:200–239
22. Gurevitch J, Hedges LV: Statistical issues in ecological meta-analysis. *Ecology* 1999;80:1142–1149
23. Rosenberg MS, Adams DC, Gurevitch J: *MetaWin: statistical software for meta-analysis version 2.0*. Sunderland, MA, Sinauer Associates, Inc, 2000
24. Borenstein M, Hedges LV, Higgins JPT, et al: *Introduction to meta-analysis*. West Sussex, UK, John Wiley and Sons, Ltd, 2009
25. Arnquist G, Wooster D: Meta-analysis: synthesizing research findings in ecology and evolution. *Tree* 1995;10:236–240
26. Eggleston RB, Mueller PO: Prevention and treatment of gastrointestinal adhesions. *Vet Clin North Am Equine Pract* 2003;19:741–763
27. Kelmer G: Update on recent advances in equine abdominal surgery. *Vet Clin North Am Equine Pract* 2009;25:271–282
28. Smith CL, Dowling BA, Dart AJ: Recent advances in equine abdominal surgery. *Vet J* 2005;170:41–51
29. Southwood LL, Baxter GM: Current concepts in management of abdominal adhesions. *Vet Clin North Am Equine Pract* 1997;13: 415–435
30. Walker E, Hernandez AV, Kattan MW: Meta-analysis: its strengths and limitations. *Clev Clin J Med* 2008;75:431–439
31. Yamout S, Boure LP, Theoret CM, et al: Effects of 0.03% weight/volume fucoidan solution on the prevention of

experimentally induced abdominal adhesions in healthy pony foals. Proceedings 16th Annual Scientific Meeting of European College of Veterinary Surgeons, Dublin, Ireland, 2007, p E18

32. Moll HD: Prevention of experimentally induced post surgical abdominal adhesions in the pony by use of sodium carboxymethylcellulose. MS thesis. Auburn University, 1989
33. Garg AX, Hackam, D, Tonelli M: Systemic review and meta-analysis: when one study is just not enough. *Clin J Am Soc Nephrol* 2008;3:253–260
34. Nuesch E, Trelle S, Reichenback S, et al: Small study effects in meta-analysis of osteoarthritis trials: meta-epidemiological study. *BMJ* 2010;341:c3515
35. Zhang A, Ni H: Small studies may overestimate the effect sizes in critical care meta-analyses: a meta-epidemiological study. *Crit Care* 2013;17:R2
36. Abbas M, Nafeh AE, Elsebae M, et al: Dose related effect of systemic antibiotics in prevention of postoperative intra-abdominal adhesion formation in experimental animals. *J Egypt Soc Parasitol* 2008;38:813–822
37. Nishimura K, Nakamura RM, diZerega GS: Ibuprofen inhibition of postsurgical adhesion formation: a time and dose response biochemical evaluation in rabbits. *J Surg Res* 1984; 36:115–124
38. Oncel M, Kurt N, Remzi FH, et al: The effectiveness of systemic antibiotics in preventing postoperative, intraabdominal adhesions in an animal model. *J Surg Res* 2001; 101:52–55
39. Zeng Q, Yu Z, You J, et al: Efficacy and safety of Seprafilm for preventing postoperative abdominal adhesions: systematic review and meta-analysis. *World J Surg* 2007;31:2125–2131
40. Chaturvedi AA, Lomme RM, Hendriks T, et al: Prevention of postsurgical adhesions using an ultrapure alginate-based gel. *Br J Surg* 2013;100:904–910
41. Lou W, Zhang H, Ma J, et al: In vivo evaluation of in situ polysaccharide based hydrogel for prevention of postoperative adhesion. *Carbohydr Polym* 2012;90:1024–1031
42. Burkhard MJ, Baxter G, Thrall MA: Blood precipitate associated with intra-abdominal carboxymethylcellulose administration. *Vet Clin Path* 1996;25:114–117
43. Dumond P, Franck P, Morisset M, et al: Pre-lethal exposure to carboxymethylcellulose confirmed by identification of specific IgE-review of the literature. *Eur Ann Allergy Clin Immunol* 2009;41:171–176
44. Kumar S, Wong PF, Leaper DJ: Intra-peritoneal prophylactic agent for preventing adhesions and adhesive intestinal obstruction after non-gynaecological abdominal surgery (review). *Cochrane Database Systematic Reviews* 2009. doi: 10.1002/14651858.CD005080.pub2
45. Robertson D, Lefebvre G, Leyland N, et al: Adhesion prevention in gynaecological surgery. *J Obstet Gynaecol Can* 2010;32:598–608