

The use of intra-abdominal carboxymethylcellulosis

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Peritoneal adhesions, abnormal fibrous bands between bowel segments or between the intestine and the abdominal wall, cause a major concern in human (1) (2) and equine abdominal surgery and can lead to chronic abdominal pain, to severe recurrent colic and death (3). The incidence of adhesion formation in human medicine is well established considering that nearly every abdominal surgery causes adhesions (4) but not all adhesions were clinically significant. A huge follow-up study during a ten year period showed that the incidence of small bowel obstructions caused by adhesions from previous abdominal surgery is about 6 % in humans (5) and that over 30 % of people will be rehospitalized due to sequelae from an abdominal surgery (6). In horses the proportion of clinically significant adhesions is estimated to be higher than in humans, varying from 13 to 27 % (7) (8) but the precise incidence is hard to establish as a lot of cases with recurrent colic after previous laparotomy are managed medically or not subjected to necropsy (9). In humans, lower abdominal surgery seems to cause the highest incidence of adhesions (5) whereas in the equine patient, small intestinal lesions are of increased risk (10) (11). The mechanism of adhesion formation has been extensively studied in experimental and clinical studies (12). Serosal lesions during abdominal surgery are covered by fibrin, and in presence of blood and inflammation, the fibrinolysis diminishes by the increase of plasminogen activator inhibitor. The fibrin is subsequently invaded by fibroblasts and vessels, which leads to the formation of fibrous bands (13) (14) (15). In order to study the efficacy of preventive treatments, different experimental models for the induction of adhesions in horses have been developed, using serosal abrasion and suture placement (16) (17) (18) or creation of vascular lesion (19) or small intestinal resection (20). As adhesions are favoured by serosal lesions and the presence of blood, the most important prevention is proper surgical technique, gentle handling of the intestine and good haemostasis (15) (21) (22).

Carboxymethylcellulose (CMC), a high-molecular weight, substituted polysaccharide, can be formulated as a liquid or a gel. Most studies evaluated sodium CMC (SCMC) but one study showed that Zn⁺ modified SCMC slows the resorption of CMC from the peritoneal cavity (23). The rationale of CMC is to protect the serosa during intestinal handling and to obtain flotation of the intestine after surgery to reduce the risk of serosal attachment between different intestinal loops. The liquid must remain at least 36 h and best up to 7 days (24) in the abdomen in order to allow complete serosal healing. The quick resorption of irrigation fluid by the peritoneum does not give protective effect to Ringer lactate or saline (25) (24). Carboxymethylcellulose is used as 1 up to 4 % solution and is also combined with other anti-adhesion agents to increase its effect. In order to increase fibrinolysis, tPlasminogen Activator (tPA) or heparin are combined with CMC (26) (27). For inflammation reduction, dexamethasone is used locally with CMC (28). These treatment combinations showed improved protection from adhesions in experimental animals but are not yet applied in clinical studies. In laboratory animals, CMC has been associated with reduction of adhesions in some studies (29) (30) but others did not show beneficial effect or increase of bleeding in case of adhesiolysis (31). Other conflicting results are increased risk of anastomotic failure in the colon of rats (32) and propagation of infection in case of septic peritonitis (33). Therefore, carboxymethylcellulose alone is not commonly used in human medicine and no commercially available specialty is licensed in Europe or the USA. Other agents like barrier membranes containing CMC in combination with hyaluronic acid (HA) commercialized as Seprafilm™ have been largely used in human medicine and several

clinical trials showed favourable effects (34) (35) (36) (37). Again, intestinal anastomosis leakage seems to be increased with membrane coverage and Seprafilm is contra-indicated for resection and anastomosis sites (38) (39).

In experimental studies in horses, the negative effect on the healing of anastomoses on jejunum has not been observed with CMC or CMC-HA membrane (20). These products even seemed advantageous by adhesion reduction (40). In Horses, the effect of adhesion barriers was evaluated in a limited number of experimental studies with a small number of individuals in treatment and control groups. Some studies showed advantageous effects (16) (40) (18) (41) whereas CMC did not show significant reduction of adhesions in treatment groups in other studies (42) (43) (44). Nevertheless, the meta-analysis of Munsterman and coworkers (45) on the effect of adhesion barriers regrouping the above-mentioned studies about CMC and other studies about the use of the HA-CMC membrane (20) and fucoidan (46) showed that treated animals were 10 times less likely to develop adhesions than the untreated controls. Except in the studies of Moll (1991), Lopes (1998) and Sullins (2010), horses received non-steroidal anti-inflammatory (NSAIDS) medication as well as peri-operative antibiotics. As NSAID's or antibiotics (47) (48) have shown protective effect from adhesions, the effect of adhesion barriers may be improved by addition of these perioperative medications (45), explaining partly the difference in the results.

Clinical studies on the effect of adhesion barriers are scarce in horses. In most of the client-owned cases no definite diagnosis of postoperative adhesions has been made (by relaparotomy, laparoscopy, or necropsy) and the outcome variables were essentially based on recurrence of colic and long-term survival. The study of Mueller (49) did not show any difference between CMC treated and control horses whereas another study using historical control cases during a 12-year period, showed improved survival rates in CMC treated horses suffering small intestinal lesions (50). Two other clinical studies in horses evaluated the safety of the HA-CMC membrane covering a small intestinal anastomosis (51) (52) and reported no negative effect like anastomotic failure. However, these studies failed to show a significant valuable effect of the adhesion barrier. Finally omentectomy has been associated with less adhesion formation in a study in which no other adhesion barrier was used (53).

In conclusion, the results obtained in experimentally induced adhesion studies in normal animals may differ from the results in clinical cases due to the lack of peritoneal inflammation, endotoxemia and severely distended small intestine more prone to adhesions. In addition, the results from human studies cannot be transposed completely to horses due to the huge difference of the digestive tract between species. Therefore, large randomized clinical trials are warranted for determining more objectively the best adhesion prevention strategy in order to improve short- and long-term survival after equine abdominal surgery.

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