3 INTRODUCTION

3.1 Colic in horses and its importance

In horses, colic is an important disease and one of the most frequent causes of death (TRAUB-DARGATZ *et al.* 2001). The annual incidence in the horse population has been reported as 4-10 colic events/100 horses per year (TINKER *et al.* 1997, KANEENE *et al.* 1997) with a case fatality rate of 11%, and 1.4 % of colic events resulting in surgery. Beside the fatality rate of colic, the event is also associated with a high economic burden with an estimated annual cost of $115,300,000 in the USA (TRAUB-DARGATZ *et al.* 2001). In most cases of colic (approx. 80-85%) the horses respond well to medical treatment or resolve spontaneously (WHITE 2009) and obstructing or strangulating diseases requiring surgery only represent 2 to 4 per cent of colic cases (WHITE 1990). Reported short-term survival rate (to discharge) in literature is between 49,4 % and 88% depending on the year of the study and population examined (HUNT *et al.* 1986, PASCOE *et al.* 1983, PHILLIPS and WALMSLEY 1993, FUGARO and COTÈ 2001, SEMEVOLOS *et al.* 2002, FREEMAN *et al.* 2000). Long-term survival rates are varying between 66 % and 84% (SEMEVOLOS *et al.* 2002, MAIR and SMITH 2005c, PHILLIPS and WALMSLEY 1993, FREEMAN *et al.* 2000).

3.1.1 Complications after colic surgery

Complications after colic surgery are dependent on the involved intestinal segment (MAIR and SMITH 2005a). After small intestinal surgery and possibly anastomosis frequent complications are anastomotic obstructions, postoperative ileus (POI) and adhesions (FREEMAN *et al.* 2000, VAN DEN BOOM, R. and VAN DER VELDEN 2001). After large intestinal surgery, recurrence of the disorder, endotoxaemia, progression of ischaemia and peritonitis are some of the complications, which can occur after surgery (FREEMAN 2010).

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3.1.1.1 Postoperative ileus (POI)

The prevalence of POI in horses after colic surgery has been reported as 10 to 19 % (FREEMAN *et al.* 2000, COHEN *et al.* 2004) and up to 27% after small intestinal surgery (HOLCOMBE *et al.* 2009). Risk factors associated with an increased likelihood of developing POI include small intestinal lesions, high PCV at admission, more than 8 L reflux at admission, high heart rate at admission, and increased duration of anaesthesia (COHEN *et al.* 2004, TORFS *et al.* 2009, TORFS 2012). Factors which may reduce the odds of developing POI includes pelvic flexure enterotomy and intraoperative administration of lidocaine (COHEN *et al.* 2004).

The POI in horses is characterized by gastrointestinal reflux, small intestinal distension, haemoconcentration, tachycardia and abdominal pain (TORFS 2012). Beside the longer recovery time phase after colic surgery, POI is associated with a higher complication rate, higher financial costs, and in some cases mortality rate (HOLCOMBE *et al.* 2009). The rate of POI after colic surgery is dependent on the population studied with the higher prevalence after small intestinal lesions with a reported rate of 10% to 33% (FREEMAN *et al.* 2000, HOLCOMBE *et al.* 2009, TORFS *et al.* 2009). A higher rate of POI with 30% is reported after resection of damaged intestine after small intestinal lesions compared to a rate of 15% in horses with small intestinal lesions without resection. The rate of POI after colic surgery without distinguishing between small and large intestinal lesions is reported to be 13.7% (MAIR and SMITH 2005b).

In a study by TORFS *et al.* (2009) the reported survival rate of horses with POI to discharge after colic surgery because of small intestinal lesions was 34%.

3.1.1.2 Endotoxaemia

In the equine intestinal tract there is a large resident population of gram-negative bacteria. This serves as a reservoir of endotoxin, normally confined to the lumen of the healthy intestine by the protective mucosal barrier (MORRIS 1991). If the intestinal wall is injured as in cases of acute gastrointestinal diseases with mural inflammation or ischaemia (such as volvulus coli), the endotoxin gains access to the

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circulation. Through the release of lipopolysaccharide (LPS) from gram-negative bacteria and subsequent interaction with the immune system, many endogenous inflammatory mediators such as interleukins, TNF-α and prostaglandins are released into the circulation (MORRIS 1991, SMITH *et al.* 2005). The presence of endotoxin within the blood is called endotoxaemia (MOORE 2001). Clinical signs of endotoxaemia in the horse are dependent on the stage of the disease. In the early hyperdynamic phase of endotoxaemia, pulmonary hypertension and ileus are present with clinical signs of depression, restlessness, tachycardia, and colic. In the hypodynamic phase of endotoxaemia, the depression and anorexia are accompanied by fever, hyperaemic mucous membranes, prolonged capillary refill time, and hypotension caused by decreased systemic vascular resistance caused by the release of prostaglandins (BOTTOMS *et al.* 1981, LAVOIE *et al.* 1990). In severe cases, the endotoxaemia can result in collapse, SIRS, DIC and laminitis (MOORE 2001). A typical laboratory finding is a profound neutropenia with toxic neutrophil morphology (presence of Döhle bodies) and a left shift (BARTON and PERONI 2012).

The clinical management of endotoxaemia includes reduced transfer of endotoxins into the blood circulation by administering smectite orally to absorb bacterial toxins and bacteria and by removing the source of endotoxins (such as the ischaemic intestine). After endotoxins have entered into the circulation, the most effective treatment is the binding and neutralisation of the toxin before it can interact with the host´s receptors sites (MOORE 2001). This can be achieved through the administration of a hyperimmune serum containing anti-endotoxin antibodies or Polymyxin B (DURANDO *et al.* 1994). If the inflammatory cascade has been activated and clinical signs are present, additionally administration of NSAIDs is indicated to prevent further release of prostaglandins (KELMER 2009). Additionally, supportive fluid therapy to prevent cardiovascular shock as a result of the endotoxaemia is recommended.

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3.1.1.3 Adhesion formation

A frequent long-term complication after colic surgery is adhesion formation with a reported incidence of clinically relevant adhesions requiring additional surgery or euthanasia as high as 22.1% in a population of horses after small intestinal surgery (*et al.* 1990) and of 28.2% in a population of horses after colic surgery (GERHARDS 1990). The risk of adhesions is reported to be higher in juvenile horses after surgery (LUNDIN *et al.* 1989). However, a study by SANTSCHI *et al.* (2000) found only 8 % adhesions in foals which recovered after the first laparotomy. The adhesion formation was related to the initial lesion causing colic and the age of the foal at first surgery. The highest risk of adhesion was found in suckling foals (15 days-6 months). Another study by VATISTAS *et al.* (1996) identified adhesions in 17% of the foals studied, which recovered from anaesthesia after laparotomy but were subsequently subjected to euthanasia because of recurrent colic.

The relationship between the primary site of the lesion and the site of adhesion formation in adult horses is not always related (GERHARDS 1990, GORVY *et al*. 2008). In the study of GORVY *et al.* (2008) a prevalence of adhesion of 32% was found at re-laparotomy with no association between the site of the original lesion or the performance of an intestinal resection at the first surgery and subsequent adhesion formation.

Different techniques are used to prevent adhesion formation including good tissue handling skills during surgery, frequent moistening of the exposed viscera, intra-operative lavage, avoiding exposed suture on the serosal surface of the bowel, minimizing contamination, applying aseptic surgical techniques, minimal tissue trauma, and omentectomy (SOUTHWOOD *et al.* 1997). Postoperatively, low-dose heparin therapy (PARKER *et al.* 1987) and appropriate use of antimicrobials and anti-inflammatory drugs have been suggested to prevent adhesion formation (SANTSCHI *et al.* 2000, SMITH *et al.* 2005a). The use of new surgical material and techniques such as carboxymethylcellulose, bioresorbable patches and indwelling abdominal drains for peritoneal lavage have been suggested to decrease adhesion formation after laparotomy (SMITH *et al.* 2005a).

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3.1.1.4 Other complications

After colic surgery, other common non-fatal complications include jugular vein thrombosis and ventral midline incisional infection (PROUDMAN *et al.* 2002, FREEMAN 2003). In some case, laminitis also occurs, especially in cases of severe endotoxaemia (FREEMAN 2010). Horses with DIC are predisposed to the development of jugular vein thrombosis (DIAS and NETO 2013).

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3.2 Postoperative ileus (POI) in the literature

3.2.1 Definition

In human medicine, POI is defined as “a transient cessation of coordinated bowel motility after surgical intervention, which prevents effective transit of intestinal contents and/or tolerance of oral intake” (DELANEY *et al.* 2006). Clinical symptoms usually include abdominal pain, nausea and vomiting, distension and bloating, delayed passage of flatus and stool, and an inability to progress to an oral diet (BOECKXSTAENS and DE JONGE 2009). The duration of POI correlates with the degree of surgical trauma and is most severe after colonic surgery (DELANEY *et al.* 2006). Most cases rapidly resolve after few days but in complicated cases resolution may take days to weeks. This is associated with a high economical importance in the health system in human medicine (IYER *et al.* 2009).

In equine medicine POI has been defined as a nasogastric reflux volume > 20 L during a 24-hour period after surgery or a reflux volume > 8 L at any single sampling time after surgery (ROUSSEL *et al.* 2001). Clinical signs in horses with POI include abdominal pain, absence of gastrointestinal sounds, absence of defecation, and accumulation of stomach fluid (ROUSSEL *et al.* 2001). The treatment of POI in horses is cost-intensive with a high morbidity and mortality rate, ranking first among fatal postoperative complications in horses after colic surgery with a reported survival rate to discharge of only 34% (TORFS *et al.* 2009).

3.2.2 Aetiology

Previous studies in animal models have suggested two major mechanisms involved in the development of POI: neurogenic and inflammatory mechanisms both related to the surgical procedure itself (BOECKXSTAENS and DE JONGE 2009). These two mechanisms probably combine in causing POI with different time frames, considerable overlap, and possible interactions (BAUER *et al.* 2002). A third component discussed in the development of POI, is the effect of different drugs (e.g. anaesthetics) on the motility of the intestine after surgery (KEHLET 2008). However,

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the effects of volatile anaesthetics is short lasting and therefore only of marginal importance. Perioperative use of sedatives as alpha-2-agonists (e.g detomidine) can affect the motility of the gastro-intestinal-tract and gastric emptying (SUTTON *et al.* 2002). The combined use of ketamine and xylazine for induction of anaesthesia in horses resulted in a complete loss of intestinal motility for 3-6 hours (SINGH *et al.* 1996). The use of post-operative opioids as pain treatment has a greater impact on the gastro-intestinal motility, with a delayed gastric emptying and prolonged intestinal transit after administration of morphine (BOSCAN *et al.* 2006) or butorphanol (SELLON *et al.* 2004).

3.2.2.1 Neurogenic phase

The normal function of the gastrointestinal tract is dependent on the coordination of activating parasympathetic stimuli and inhibition though sympathetic activation. Through hyperactivation of the autonomic nerve system in the early postoperative phase with an increased sympatheticus activity the motility of the intestine is decreased (MIEDEMA and JOHNSON 2003). The degree of inhibition of motility is dependent on the severity of the stimuli, with only a short-term inhibition of motility after skin incision and laparotomy through activation of a low-threshold adrenergic inhibitory pathway (BOECKXSTAENS and DE JONGE 2009). This probably involves a spinal loop with afferent splanchnic nerves synapsing in the spinal cord and efferents travelling back to the entire intestinal tract, abolishing the motility of the entire gastrointestinal tract (LIVINGSTON and PASSARO 1990). In contrast, more intense stimuli such as handling and manipulation of the intestine lead to an activation of high-threshold supraspinal pathways with a much longer inhibition of intestinal motility (BARQUIST *et al.* 1996, BOECKXSTAENS *et al.* 1999). This includes activation of additional pathways actively mediated by the brainstem. After transmission of afferent signals to the brainstem, the signals trigger an increased autonomic output to the neurons of the intermediolateral column of the thoracic cord to the location of sympathetic preganglionic neurons. Activation of these nerves subsequently inhibits the motility of the entire gastro-intestinal tract through the effect of secreted noradrenaline on adrenergic receptors and subsequently inhibition of the

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migrating motor complexes (MMC) (SAGRADA *et al.* 1987, BOECKXSTAENS and DE JONGE 2009). Additionally, intense stimulation of the splanchnic afferents triggers an inhibitory non-adrenergic, vagally mediated pathway (THE *et al.* 2005).
The role of neurogenic activation for the development of POI is important, but is not the only contributing factor as it cannot explain the long-lasting dysfunction of the intestinal motility in some cases (PANTELIS and KALFF 2007).
The “first” or neurogenic phase usually ceased at the end of surgery (BOECKXSTAENS and DE JONGE 2009).

3.2.2.2 Inflammatory phase

In 1978 FIORAMONTI and RUCKEBUSCH observed two phases of inhibition of intestinal activity in dogs and sheep after abdominal surgery. The first phase consisted of complete inhibition of electrical spiking activity during and after surgery, which transiently ceased after the end of surgery. The second phase of inhibition was observed 3-4h after surgery with the duration being dependent on the nature of surgery, with a long-lasting reduction (48-72h) of spiking activity after resection of the small intestine in dogs and sheep (BUENO *et al.* 1978a). It could be demonstrated, that an inhibitory neural pathway mediated the first phase; however the exact origin of the second phase was unclear.
KALFF *et al.* (1998) suggested that the timeframe of the second phase of POI correlates with an activation and infiltration of inflammatory cells in the intestinal wall. Intestinal manipulation resulted in the activation of macrophages and subsequent release of cytokine and chemokine with an influx of leukocytes approx. 3-4h after surgery. Other authors demonstrated an interaction between the immune system, the autonomic nervous system and the muscular function of the gastrointestinal tract (BOECKXSTAENS *et al.* 2009, DE WINTER and DE MAN 2010, WEHNER *et al.* 2012).
Discussed mediators involved in the pathogenesis of inflammatory-mediated ileus include nitric oxide (NO) and prostaglandins (DE WINTER and DE MAN 2010). The inducible form of NO synthase (iNOS) has been suggested to mediate LPS-induced motility disturbances in mice models of sepsis-induced ileus (DE WINTER *et al.*

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2002, 2005) and in surgically induced POI (KALFF *et al.* 2000). There was evidence, that the effects of iNOS on motility disturbances in septic induced ileus were partly mediated by NO-mediated oxidative stress mechanisms, by the use of anti-oxidant molecules (DE WINTER *et al.* 2005). In a study by SCHWARZ *et al.* (2001) surgical manipulation of the intestine of rats resulted in an expression of COX-2 mRNA and proteins within resident muscularis macrophages, together with an increased prostaglandin level in the peritoneal fluid and in the circulation. The expression of COX-2 mRNA was associated with a decrease of jejunal circular muscle contractility in-vitro and increased gastrointestinal transit time. Both of these could be alleviated pharmacologically by the use of a selective COX-2 inhibitor (DFU (phenyl-2(5H)-furan one)). In humans, KALFF *et al.* (2003) also demonstrated an expression of COX-2 mRNA in the muscularis externa of jejunal specimens after prolonged abdominal surgery (approx. 3h). In addition to the local effect on gastrointestinal motility, prostaglandins are suggested to modulate afferent nerve signalling from the intestine to the spinal cord and higher brain centres, Thereby modulating sensitivity disturbances and pain signalling pathways (WANG *et al.* 2005).

Manipulation of small intestine in rodents resulted decreased contractility compared to control specimens, which was accompanied by an accumulation of neutrophilic granulocytes, monocytes and mast cells in the muscularis externa and an activation of resident macrophages (KALFF *et al.* 1998).

Another study by KALFF *et al.* (2003) investigated the initiation of an inflammatory response within the human intestinal muscularis externa intraoperatively. Numerous macrophages within the intestinal muscularis externa with an expression of increased lymphocyte immunreactivity were shown after prolonged abdominal surgery (approx. 3h). This was correlated with a time-dependent expression of intestinal cytokines and enzymes (IL-6, IL-1, TNF-α, iNOS and COX-2 mRNAs). In cases of re-laparotomy 24 or 48 h after the first laparotomy, a leukocytic infiltration (neutrophils and monocytes) primarily recruited to the circular muscle layer was observed in the jejunal specimens. This was not identified in the early specimens (30 min after incision) from the first surgery. The muscle strips after re-laparotomy also demonstrated a marked

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decrease of in-vitro spontaneous activity and response of circular muscle to stimulation with bethanechol.

Type and severity of mechanical manipulations can induce various degrees of intestinal inflammation, as has been documented in rodents (KALFF *et al.* 1998, 1999 a,b, 2000, SCHWARZ *et al.* 2001, 2004, WEHNER *et al.* 2007), mice (THE *et al.* 2005), pigs (HIKI *et al.* 2006), and human beings (de JONGE and THE 2004, KALFF *et al.* 2003, THE *et al.* 2008).

3.2.3 Treatment of POI

3.2.3.1 Treatment of POI in human medicine

The concept for treatment of POI is based on a multimodal postoperative rehabilitation together with techniques to reduce the occurrence and/or duration of POI (KEHLET 2008).

3.2.3.1.1 Factors enchaining recovery after surgery:

Preventive techniques

The use of thoracic epidural local anaesthetics the first 2-3 days after laparoscopic sigmoid resection or colonic resection through an epidural catheter has been shown to reduce the duration of POI, and the use of analgesics (NEUDECKER *et al.* 1999, KEHLET and KENNEDY 2006). The use of epidural analgesia was more important after open surgery than after laparoscopy. Whenever possible the laparoscopic approach to major abdominal surgery is recommended because of the important beneficial effects as reduced pain and minimizing the inflammatory response. This also should reduce the incidence and duration of POI (KEHLET and KENNEDY 2006).

Prokinetic drugs and laxatives

TRAUT *et al.* (2008) performed an analysis of randomized controlled parallel-group trials comparing the effects and efficacy of different systemic acting pro-kinetic drugs for the treatment of adynamic postoperative ileus in adult patients. The positive

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