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Gastrointestinal Healing

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The gastrointestinal tract heals as any other tissue in an orderly manner, with an inflammatory phase, a debridement phase, a granulation phase, and a maturation phase. However, there are some characteristics very specific to the gastrointestinal tract that sets it apart from other healing tissues.

The healing process of the gastrointestinal tract should not only re-establish the anatomical integrity of the tract but also its function. Healing should happen with minimal scaring and stricture formation that could impede the motility of the gastrointestinal tract. Additionally, the formation of adhesions, even though rare in small animal surgery, could deteriorate gastrointestinal motility and should be minimized.

1.1 Anatomy

The wall of the gastrointestinal tract has a mucosa, a submucosa, a muscularis, and a serosa, except the esophagus and the distal rectum.

The mucosa has three distinct layers: the epithelium, the lamina propria and the muscularis mucosa. The lamina propria layer is made of vessels, lymphatics, and mesenchymal cells whereas the muscularis mucosa is a thin muscle layer. After completing the anastomosis, the mucosa heals very fast by epithelial cells migration over the defect providing a rapid barrier from the intestinal content. For intestinal healing to occur, a good surgical apposition of layers is required; everting or inverting patterns interfere with mucosal healing.

The submucosa layer, incorporating the bulk of the collagen, is the holding layer in intestinal surgery. Type I collagen (68%) predominates in the submucosa, followed by type III (20%) and finally collagen type V (12%) (Thornton and Barbul 1997). It is a loose connective tissue with lymphatic, nerve fibers, ganglia, and blood vessels that should be preserved during surgery. The muscularis layer consists of an inner circular muscle layer, a longitudinal outer muscle layer and collagen fibers. The serosal surface is made of connective tissue with mesothelial cells, lymphatics, and blood vessels. The serosa is important in the healing process because it helps prevent leakage of the gastrointestinal content in the immediate post-operative period.

1.2 Phases of Wound Healing

1.2.1 Partial Thickness Injury

A partial thickness injury affecting only the mucosa or the serosa heals with epithelial cells and mesothelial cells proliferation without scaring. A full-thickness trauma of the gastrointestinal tract results in an inflammatory reaction and a non-epithelial cell proliferation that can result in scaring secondary to fibroblast activity (Thornton and Barbul 1997; Thompson et al. 2006).

1.2.2 Full-Thickness Injury

As soon as the wall of the gastrointestinal tract is incised, hemorrhage occurs but it is rapidly controlled by an intense vasoconstriction. Following this initial phase, vasodilation occurs with migration of neutrophils, macrophages, platelets, and liberation of inflammatory mediators which characterizes the inflammatory phase. The platelets, by releasing diverse platelet-derived growth factors (PDGF) and cytokines, contribute to hemostasis

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and cell recruitment like macrophages and fibroblasts. The neutrophils predominate during the first 24 hours but then macrophages become predominant past 48 hours following the initial injury. The macrophages play an important role in healing of the gastrointestinal tract by controlling local infection with phagocytosis, production of oxygen radicals, and nitric oxide. They also participate in debridement with phagocytosis and production of collagenase and elastase. The macrophages also regulate matrix synthesis and cell recruitment and activation. They release several growth factors (PDGF, transforming growth factor (TGFβ), fibroblast growth factor (FGF), IGF) and cytokines (TNFα, IL-1) important for tissue healing. The macrophages recruit lymphocytes that liberate interleukin (IL-6) and interferon (IFN) and promote angiogenesis with production of VEGF (Vasculogenic Endothelial Growth Factor). Finally, the capillary permeability is increased resulting in inflammation and edema on the edges of the incision that can persist for two weeks. Care should be taken initially when the sutures are placed to not induce tissue strangulation and necrosis. A fibrin seal develops over the serosa very quickly to provide a leakage protection of the surgical site (Pascoe and Peterson 1989; Thornton and Barbul 1997; Thompson et al. 2006).

Overlapping with the inflammatory phase is the debridement phase, with removal of injured tissue by macrophages. The debridement phase should not exceed 1–2 mm from the edges of the incision. During this process, collagen is resorbed by collagenase and synthesized by smooth muscle and fibroblast. The smooth muscles are the major contributor in collagen production within the gastrointestinal tract. The collagen degrade by the collagenase activity weakens the strength of the anastomosis. In the colon, the collagenase activity is increased over the entire length of the colon while in the small intestine, it is increased only at the site of the anastomosis (Hawley 1970; Jiborn et al. 1978a). The risk of dehiscence is high between 3 and 10 days after surgery. Usually, after 4 to 5 days, collagen synthesis is superior to lysis and the anastomosis regains strength. This collagenase activity can be increased by the amount of trauma induced by tissue manipulation at the time of surgery or the presence of a foreign body, and by the degree of contamination. The amount of collagen synthesized is affected by hypotension, hypovolemia, shock, and certain medications.

The granulation tissue appears at the beginning of the proliferative phase of intestinal healing. Fibroblast is the major cell type present past day 4 after surgery. The fibroblasts migrate under the control of PDGF, TGFβ and FGF. Fibroblast and smooth muscle lay down collagen fibers and new capillaries appear in the field.

After one to two weeks following the anastomosis, the epithelial layer is fully restored. The epithelialization of the anastomosis reduces the formation of excessive fibrosis tissue secondary to inflammation. The excessive fibrosis could lead to stricture formation. During the maturation phase, the collagen fibers are reorganized and the anastomosis is becoming thinner.

In summary, an intestinal anastomosis loses bursting strength during the first 3 to 5 days to finally regain 50–70% of the initial bursting strength in 2 to 3 weeks (Jiborn et al. 1978a, 1978b; Thompson et al. 2006; Munireddy et al. 2010).

1.3 Factors Affecting Gastrointestinal Tract Healing

1.3.1 Ischemia and Tissue Perfusion

Ischemia interferes with healing of any tissue and especially the gastrointestinal tract. The oxygen delivery to the peripheral tissue depends on the anatomy of the capillaries, vasomotor control, and oxygen saturation. The tissue perfusion depends on the amount of soft tissue trauma and especially trauma to the blood supply of the loop of intestine. The placement of tight sutures interferes with tissue perfusion and may increase the risk of dehiscence, especially in the colon and esophagus (Shikata et al. 1982; Chung 1987; Jonsson and Hogstrom 1992; Thornton and Barbul 1997). Hypovolemia and hypotension are critical factors that divert blood flow to essential organs, and oxygen delivery is also very important for collagen synthesis. A partial pressure of oxygen of at least 40 mmHg is required for collagen synthesis. During a hypovolemic event, the gastrointestinal tract downregulates its own blood flow. Anemia does not interfere with healing as long as the patient has a good cardiac output to compensate (Thompson et al. 2006).

1.3.2 Suture Intrinsic Tension

Incising oral and visceral tissues stimulate an initial vasoconstriction, followed by secondary vasodilation and increased vascular permeability mediated largely by kinins, ultimately causing edema and swelling of tissue edges. This should be kept in mind when tensioning suture lines or stitches because ischemic necrosis may develop as the suture strangulates the swelling tissue. In general, sutures in viscera of the digestive tract should be tensioned such that the incision edges are held firmly together without crushing or cutting through the needle purchase. When inverting suture patterns are used, the suture line is firmly tensioned such that the incised edges are fully inverted and minimal suture is exposed on the surface of the organ (Thornton and Barbul 1997).

1.3.3 Surgical Technique

A simple apposition of the submucosa of the gastrointestinal tract is desired to achieve primary healing because it is associated with the least amount of fibrous tissue and better function. An apposition of the submucosa is important for the rapid healing of the mucosa and preventing migration of microorganisms within the surgical site. An eversion or inversion of the mucosa has been shown to interfere with primary healing (Jiborn et al. 1978a, 1978c; Jansen et al. 1981; Ellison et al. 1982; Jonsson et al. 1985; Pascoe and Peterson 1989; Thornton and Barbul 1997). Stapled anastomoses are becoming commonplace in veterinary surgery (Hansen and Smeak 2015; Duell et al. 2016; Snowdon et al. 2016). Staples do not promote better healing of the gastrointestinal tract when sepsis or ischemia are present (Thornton and Barbul 1997). Sutureless anastomoses have been performed with devices working by compressing two inverted ring of bowel (Maney et al. 1988; Corman et al. 1989; Ryan et al. 2006; Bobkiewicz et al. 2017).

1.3.4 Nutrition

The nutritional support of the patient is paramount for the healing of the gastrointestinal tract. Malnourished patients are at increased risk for dehiscence. The addition of a feeding tube is very important to support the anorectic patient in the post-operative period as the enterocytes are getting their nutrients mostly from the intestinal content traveling in the lumen. Vitamin A, C, and B6 are required for collagen synthesis. Iron and copper are also important for the cross-linking of protein and tissue healing. The enteral nutrition is beneficial for the integrity of the gastrointestinal tract and prevent bacterial translocation (Thornton and Barbul 1997; Marks 2013).

1.3.5 Blood Transfusion

A blood transfusion has been associated with an increased risk of leakage after gastrointestinal surgery. It has been postulated that blood transfusion is affecting the inflammatory phase and the migration of macrophages (Apostolidis et al. 2000; Munireddy et al. 2010).

1.3.6 Local Infection

A local infection increases protease activity, which delays epithelialization because protease resorbs growth factors required for healing. A braided suture should be avoided even if they received an antimicrobial treatment as bacteria adhere to them more than to monofilament (Chu and Williams 1984; Masini et al. 2011). Polydioxanone seems to have the lowest affinity for bacteria (Chu and Williams 1984).

1.3.7 Intraperitoneal Infection

A septic peritonitis interferes with healing of an intestinal anastomosis because it reduces collagen content at the level of the anastomosis. The combination of bacterial and neutrophil collagenases increases the collagen fibers breakdown. The collagen synthesis and deposition are reduced by the peritonitis (Ahrendt et al. 1996; Munireddy et al. 2010). The septic exudate present in the anastomosis prevents synthesis and deposition of collagen and angiogenesis (Thornton and Barbul 1997).

1.3.8 Medications

In an experiment in rats, it was shown that the administration of methylprednisolone did not affect the mechanical strength of colonic anastomosis (Mastboom et al. 1991a). However, the effect of steroids on the healing of the gastrointestinal tract is controversial (Thornton and Barbul 1997; Thompson et al. 2006).

The administration of NSAIDs after gastrointestinal surgery is also very controversial (Mastboom et al. 1991b; Gorissen et al. 2012; Bhangu et al. 2014; Collaborative 2014). The non-selective cyclo-oxygenase inhibitors seem to increase the risk of leakage after colorectal surgery (Gorissen et al. 2012). Two meta-analyses in human patients reported opposite results (Bhangu et al. 2014; Collaborative 2014). However, both of those studies have focused on colorectal surgery, which is not performed frequently in small animal surgery. In one of the studies, animal experiments were reviewed and showed that NSAID administration in the post-post-operative period increased the risk of leakage (Bhangu et al. 2014). The NSAIDs affect production of VEGF and angiogenesis. They also interfere with collagen formation and cross-linking (Inan et al. 2006; Gorissen et al. 2012). After administration of

NSAIDs, hydroxyproline concentration was significantly reduced after resection and anastomosis of the ileum. This effect was mostly present three days after surgery. Seven days after surgery, the concentration of hydroxyproline had risen again (Mastboom et al. 1991b). In a study on rats, NSAIDs increased the morbidity and mortality rates without necessarily leading to an increased risk of leakage (Mastboom et al. 1991b).

The chemotherapy drugs because of their immunosuppressant effect can negatively affect the healing of the gastrointestinal tract (Thornton and Barbul 1997).

1.3.9 Disease

There is very little evidence that diabetes interferes with gastrointestinal healing. In a rat model of diabetes, collagen synthesis was not affected. However, the bursting pressure of the intestinal anastomosis was reduced on day 3 after surgery, but this effect did not persist past day 7 (Verhofstad and Hendriks 1994; Thornton and Barbul 1997). Icterus has been shown to interfere with tissue healing (Bayer and Ellis 1976; Muftuoglu et al. 2005).

1.3.10 Large Intestine

The colon is considered by most surgeons as a rather “unforgiving” structure when it is incised and repaired, largely because of its unique healing qualities, and when leakage occurs, the results are often devastating to the animal (Williams 2012). An understanding of colonic healing is important, and incorporation of all the principles of repair are critical to reduce life-threatening anastomotic dehiscence. Healing of the colon undergoes similar phases of wound healing to those found in the skin and other tissue layers but with a number of important differences (Agren et al. 2006). During the inflammatory phase, a fibrin clot forms over the site and, although this clot has minimal strength, it is important to achieve an early “seal,” and it is vital that it remains to act as a scaffold for fibroblast migration during the early repair phase. For the first three to four days, nearly all support for the colonic repair comes from the suture or staple line. Angiogenesis and migration of fibroblasts occurs and eventually replaces the fibrin clot scaffold during days 3 and 4. It is during this stage of repair that breakdown is most likely to occur (Williams 2012).

Although a fragile mucosal bridge also occurs within the first three to four days, depending on the size of the defect, substantive wound strength occurs only when local recruited smooth muscle cells and fibroblasts from the colonic submucosa and muscularis bridge the incision and begin producing collagen. Appropriate-sized tissue bites are particularly important when repairing the colon because a zone of active collagen lysis occurs in a 1–3 mm zone immediately adjacent to the incised colon edge. The activity of matrix metalloproteases that cause collagen degradation peaks during the debridement phase through day 3 (Agren et al. 2006). Provided there is ample vascular supply after this time, collagen synthesis is accelerated, coupled with a rapid gain in wound strength. Aggressive tissue handling and excess contamination of the colonic wound can greatly increase the debridement activity at the sutured wound edge and this increases the risk of early tissue disruption, leading to dehiscence and leakage (Williams 2012). Return of strength at the healing site reaches about 75% of normal strength at four months after surgery, which is considerably slower than in the small intestine (Thornton and Barbul 1997). Surgeons can influence uncomplicated colonic healing by ensuring adequate tissue perfusion, eliminating any tension on the repair, accurately apposing colonic edges without inducing excess trauma, containing contamination, and avoiding increased intraluminal pressures by eliminating any distal obstruction (Holt and Brockman 2003; Williams 2012). Omental pedicle wraps have been advocated to reinforce the gastrointestinal repairs and support the local healing environment. Omentum may stimulate and augment angiogenesis and may also help maintain the vital fibrin clot and seal during the early phases of wound healing. The benefit of omental wraps in colonic surgery have not been proven in recent human clinical studies of colonic resection and anastomosis. However, most surgeons still recommend covering colonic repairs with omentum (Hao et al. 2008).

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