



Research Article

A NEW PORCINE MODEL FOR THE STUDY OF HIGH-RISK COLONIC ANASTOMOSES DUE TO HYPOPERFUSION

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ARTICLE INFO

Article History:

Received 5th April, 2018

Received in revised form 24th

May, 2018 Accepted 20th June, 2018

Published online 28th July, 2018

Key words:

Anastomosis, ischemia, intestine, leakage, failure, animal model

ABSTRACT

Gastrointestinal anastomosis is a common procedure, leakage brings a significant increase in mortality and morbidity (Kofoed SC *et al.*, 2014). Multiple animals models have being proposed for the study of the anastomosis leakage, the pig is one of the most appropriate. We present a new model of high-risk colo-ileal anastomosis, conditioned by hypoperfusion of the cecum. After 5 days the anastomosis were recovered. A 30% rate of anastomosis failure was found. We think that our model is effective for the study of ischemia effects on intestinal anastomosis and may be a way of reducing the number of subjects needed on studies. **Introduction:** The suture failure in intestinal surgery known as anastomotic leakage is a serious complication resulting in a significant increase of postoperative complications and mortality. The incidence of anastomotic leakage depends on several conditions such the quality of the surgical technique, the patient's conditions and whether if the suture in made involving the colon or the rectum with fecal contamination.

Methods: We present a novel experimental model of anastomotic leakage on pigs by performing a high-risk ileocolic suture on pigs. With the aim to create an ischemic condition by a selective ligation of the marginal vessels of a 5-10 cm. segment of colon at the cecum level. Afterwards, we performed a standardized hand-sewn anastomosis between the ileum and the hypovascularized colon. On the 5th postoperative day the animals were euthanized and the anastomosis were reviewed by the same surgeons. We designed the experimental model expecting a 10% incidence of anastomotic leakage s.

Results: Ten cases were included in this observational prospective study. At the second surgery e observed a 30% rate of clinically significant anastomosis leakage.

Conclusions: With the present experimental model we have validated a simple and feasible novel model in colonic surgeries for testing anastomotic failures.

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INTRODUCTION

The needed for an intestinal suture-anastomosis is one of the most common surgical procedures in colonic surgery (Ptok H *et al.*, 2007). The suture failure known as anastomotic leakage is a serious complication resulting in a significant increase of postoperative complications and mortality (Branagan G *et al.*, 2005; Buchs NC *et al.*, 2008; Kube R *et al.*, 2010; Marra F *et al.* 2009). It may present as generalized peritonitis, as a more localized abscess or as subclinical leakage that may only be recognized radiologically (Eberhardt JM *et al.*, 2009; Nordentoft T *et al.*, 2015). In addition, the presence of a leakage has a negative impact on survival after surgery (Law WL *et al.*, 2007; Walker KG *et al.*, 2004).

The incidence of anastomotic leakage depends on several conditions such the quality of the surgical technique, the patient's conditions and whether if the suture is made involving the colon or the rectum with fecal contamination (Thornton M *et al.*, 2011). Due to obvious ethical issues, the study of the anastomotic failure on human has some limitations as there is a relative low rate of failure's incidence on standard clinical practice that force to have big numbers of subjects to obtain statistical results.

On this context, the experimental studies on animals will eliminate some of the ethical limitations, but without additional gestures to promote the failure, the rate of incidence is, like on humans, still low (McArdle CS *et al.*, 2005). This situation promotes the research on novel experimental models on animals to test the anastomotic failure (Pommergaard HC *et al.*, 2011; Rutegard M *et al.*, 2012).

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The aim of this study is to present an experimental model of intestinal anastomosis on pigs with a high possibility of developing anastomotic leakage. This model based on a selective ligation of the vessels of the cecum to create ischemia mimics the situation of performing a high-risk suture on patients with intestinal diseases.

MATERIAL AND METHODS

A prospective, randomized experimental study was carried on in male “Large White” pigs, making a standard latero-lateral, ileo-cecal anastomosis, bypassing the ileocecal valve, with the same technique that in our regular practice on humans except for a previous devascularisation of the cecum area with a vascular ligature.

We performed the procedure on 10 male “Large White” pigs between 25 and 35Kg. All procedures were performed under general anaesthesia using Ketamine, Fentanyl and Sevoflurane. A prophylactic dose of Cefotaxime 2g was administrated during the anaesthesia induction, afterwards, the standard antiseptic measures and surgical drapes were placed. Then, a median laparotomy and a peritoneal cavity exploration were performed identifying the terminal ileum and the cecum. The next step was to perform a devascularisation of the last 10-15 cm. of the cecum area with a vascular ligature on the marginal artery (Fig. 1a). We performed an anastomosis on the same way that in our regular practice; sutures were done between the middle third of the caecum devascularized zone on one side and the terminal ileum on the other side, in a latero-lateral fashion (Fig. 1b), with a 2cm opening, using a monoplane resorbable monofilament continuous suture (3/0 Biosyn, Covidien). Finally, the laparotomy was closed with a continuous suture on the fascia and skin staples.

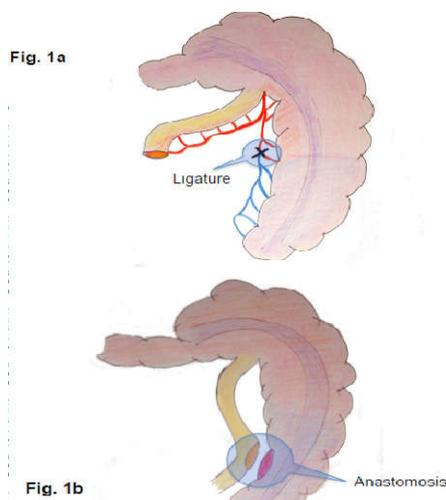


Figure 1 Colonic devascularisation (a) and anastomotic conformation (b).

On All animals were stabled in our experimental institute, on supervised and climate controlled cubicles, restarting oral intake on the first postoperative day, with free access to water and standard commercial fodder mixed with 600mg of Ibuprofen every 12 hours. Basal temperature and a physical exploration were performed to assure the welfare and clinical evolution of the animals.

On 5th postoperative day all subjects were sacrificed, then revised, first exploring the abdominal cavity searching for adhesions, signs of peritonitis, abscess or faecal contamination, classifying those findings, and then resecting the anastomoses including at least the last 10cm on each intestinal stump.

Then we proceed to euthanatize the subjects with an overdose of the anaesthetics agents. All specimens were sent to the Pathology department and a microscopic analysis of the anastomosis was performed for assessing microabscess, microscopic leakage, neovascularization and cellularity. We designed the experimental model expecting a 10% incidence of anastomotic leakages.

RESULTS

All 10 procedures were performed without complications, and during the stabled time all animals had a normal behaviour, admitting the diet and medication normally, and even having regular bowel movements on all the subjects.

From a macroscopic point of view, 3 animals had a macroscopic leakage, with local abscess and faecal contamination as the major findings, without distant or diffuse peritonitis. The most frequent adhesion indexes were 1 and 3 (Table 1), with apparent not statistical significant relation to the anastomotic leakage, probably because of the small size sample.

The microscopic study showed a polymorphonuclear dominance (median of 83,5%), 6 cases had important neovascularization, without relation with the presence of leakage. All the samples had signs of necrosis, with no difference on frequency between the focal or disseminate form.

Table 1

ID	Leak	PMN	Lymp	Vessels	Fibroblast	Macrophages	Necrosis	Haemorrhage
1	No	80%	10%	Neoformed	++	10%	Focal	Diffuse
2	No	95%	5%	Mature	+++	< 2%	Extensive	Focal
3	No	95%	5%	Mature	++	< 2%	Extensive	Focal
4	No	65%	35%	Neoformed	++	< 2%	Focal	Diffuse
5	No	95%	5%	Neoformed	++	< 2%	Focal	Diffuse
6	Si	90%	10%	Neoformed	++	< 2%	Focal	Diffuse
7	Si	70%	30%	Mature	+++	< 2%	Extensive	Limited
8	No	85%	15%	Mature	+++	<2%	Extensive	Limited
9	No	75%	25%	Neoformed	++	5%	Focal	Limited
10	Si	85%	15%	Neoformed	++	< 2%	Extensive	Diffuse

CONCLUSIONS

Our experimental study is a simple, feasible and non-expensive model for the study of anastomotic leakages in colonic surgeries. The model mimicked routine clinical situations on humans with an observed rate of 30% of leakages, and it could help in the reductions of animal subjects needed, investigation of new treatments to prevent anastomotic failure and in the costs reduction of further clinical studies.

Acknowledgments

This study is in accordance with the European Animal Experiment Legislation, controlled by the Madrid Community experimental animals welfare office and has been registered with number 10/129734.9/14. The study has also been reviewed and approved by the Ethical Review Board of our institution.

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content. The authors declare no conflict of interest. Funds were provided by Takeda Pharmaceutical, however, we do not have any contractual relation with the company and had complete liberty on the study design and elaboration.

We do not have any other relationships or activities that could appear to have influenced the submitted work.

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How to cite this article:

Carlos Garcia-Vasquez *et al* (2018) 'A New Porcine Model for the Study of High-Risk Colonic Anastomoses Due to Hypoperfusion', *International Journal of Current Advanced Research*, 07(7), pp. 14106-14108.
DOI: <http://dx.doi.org/10.24327/ijcar.2018.14108.2546>
