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Methods of securing sutures in digestive surgery
PHD THESIS SUMMARY

Scientific coordinator:
UNIV. PROF. DR. DĂNUŢ VASILE

PhD student:
CONSTANTIN BUDIN

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CONTENTS

SUMMARY

The fast evolution of multiple medicine related branches transforms digestive surgery from a "reserved", "shy" specialty to a radical one, often ended with wide, multiple organs resections.

However, the widening of the indication horizon and the increase in the number of treated patients remain marked by the complications that appear in the immediate postoperative or distant period, of which, the most feared for digestive surgery, remains the anastomotic leak (AL).

The severity of this complication explains the large number of studies aimed at identifying risk factors, detecting predictive elements, finding methods for improving local conditions, evaluating early diagnostic methods and therapeutic solutions.

By clearly setting goals (studying the risk factors for developing AL, defining the patient at risk, evaluating the benefits of using suture or anastomosis securing techniques in the digestive tract), the whole thesis tries to answer the questions "In which way the risk factors affect the incidence of AL?", "What factors and to what extent do they favor the appearance of fistulous complications? "," When is an anastomosis safe? " and "Does the reinforcement techniques and adhesives can prevent these complications?".

The thesis is structured in 2 distinct parts.

The first part - "General Part" comprises 3 chapters and represents a descriptive analysis of achievements in the field, based on laborious documentation.

Chapter 1 discusses the subject of digestive anastomoses, describes the main technical types, analyzes and compares types of sutures, anastomotic assemblies, used materials, benefits and disadvantages of each technique, using national and international studies, sometimes with contradictory results.

Chapter 2 records a variety of commonly used or experimental techniques, all aimed at increasing the safety of the suture or anastomosis line, and therefore the safety of the patient. The results regarding the efficiency of the large omentum, bovine pericardium, polypropylene mesh, various classes of adhesives, but also methods of protection of anastomoses by intraluminal devices, transanal decompression devices or endoscopic methods were analyzed and compared.

Chapter 3 examines the evolution of the definition of AL, highlighting the narrow nature of the one proposed by the UK Surgical Infection Study Group in 1991 and the superiority of the definition proposed by Kingham TP in 2008, which combines clinical signs with biochemical markers and imaging signs.

ALs are analyzed according to the time of onset and grouped into very early AF (occurring in the first 5 days postoperatively), early AF (AF occurring less than one month postoperatively), and late AF (occurring more than one month from the time of surgery), this classification highlighting the severity of very early AF and the need for immediate treatment (including relaparotomy).

The classifications of ALs according to the etiology, the clinical resonance according to the recommendations of the International Rectal Cancer Study Group (grades A – C ALs), flow, the level at which externalization occurs (anatomical classification) were described.

More than 22 risk factors mentioned in other studies were analyzed and the veracity of the data was compared with other papers addressing the same topic. The most frequently mentioned were: sex, old age, smoking, neoplastic disease, malnutrition, diabetes, cardiac, respiratory or renal comorbidities, ASA class, duration of surgery, perioperative need for transfusion. Many of the mechanisms involved are not known or have been incompletely elucidated.

Delays in diagnosis and treatment are associated with unfavorable patient outcomes (increased length of hospital stay, negative impairment of postoperative morbidity and mortality, increased economic impact).

The possibility of preoperative risk assessment could dictate the surgical technique, helping the team involved in treating the case to adopt an attitude with a higher degree of safety for the patient, even if this involves multiple, spaced in time interventions, and with a degree of (temporary or permanent) discomfort for the patient (such as resections with stoma).

The second part - “Personal Contributions” is based on the importance and the actuality of fistulous complications in digestive surgery, elements that emerge from (1) the evolution of surgical techniques and the extension of the range of indications that require (sometimes large) resections in patients with precarious biological status, (2) the relatively constant incidence of AL in recent decades, (3) the severity of AL, assessed by the morbidity, mortality, psychological and financial associated impact.

The entire content of the second part is structured around 4 main objectives: assessing the incidence of fistulous complications, studying and analyzing the potential risk factors associated with AL, developing a preoperative risk quantification system for the development of AL (identifying the patient at risk for AL) and the study of the mechanical properties conferred by synthetic, cyanoacrylates (CA) class adhesives applied at the level of sutures and digestive anastomoses.

These objectives were achieved conducting 3 descriptive, retrospective studies at the 1st Department of General and Emergency Surgery of the University Emergency Hospital in Bucharest, and an experimental study.

The first study, called "Hypocalcemia - a possible risk factor for anastomotic leak in digestive surgery" was conducted in 2015-2019 and included a total of 122 consecutive patients whose surgical treatment involved performing at least one suture or anastomoses in the infradiaphragmatic digestive tract.

This study showed lower levels of serum calcium in patients admitted to the emergency department (8.21 ± 0.7 mg/dL, $p = 0.01$) and in patients with fistulous complications (8.07 ± 0.82 mg/dL, $p = 0.01$).

Considering the normal range of serum calcium between 8.5 mg/dL and 10.5 mg/dL, hypocalcemia was shown to favor the appearance of AL (15.9% vs 1.3%, $p = 0.002$).
Given the resulting data, the study concluded that hypocalcemia may be a risk factor for fistulous complications, and the accuracy of the data needs to be confirmed in larger groups of patients.

The second study, "Study of risk factors involved in the occurrence of anastomotic leak" analyzes a number of risk factors published by Romanian and foreign authors, but also proposes new factors that may be associated with the occurrence of AL.

Results from a total number of 526 anastomoses and 96 sutures showed that atherosclerotic disease, obesity, diabetes mellitus, heart rhythm disorders such as atrial fibrillation, heart failure, the presence of metastatic disease were correlated with a higher risk of developing AL ($p < 0.05$). For sex, hepatopathies, nephropathies and oncological history of the patient, an association cannot be demonstrated ($p > 0.05$).

Nutritional status was studied by the values of total serum proteins, serum albumin, triglycerides, cholesterol, calcium. With the exception of hypocalcemia (serum Ca < 8.5 mg/dL)

and hypertriglyceridemia (serum triglycerides > 150 mg/dL), the other variables did not show any association with the occurrence of AL.

Other associated risk factors were: severe form of anemia, obstructive syndrome, presence of peritonitis, need for vasopressor/inotropic support.

There were no significant differences related to the surgical technique, comparing the anastomoses with separate or continuous threads, various types of anastomotic assemblies (T-T, T-L, L-T, L-L), the variety of anastomosed segments, handsewn and mechanical anastomosis.

This study concludes that AL has a multifactorial etiology, each factor influencing differently the unfavorable evolution of the anastomosis.

The third study ("FISTULA SCORE – a predictive tool for the occurrence of anastomotic leak") was aimed to quantify the risk assigned to each risk factor and develop a system to identify the patient at risk for fistulous complications.

Based on the odds ratio determined for each risk factor, we proposed a preoperative assessment score of the general risk, called FISTULA SCORE, an acronym that comes from joining the first letters (in English) of the included risk factors.

The significance threshold value equal to 4 points gives the test a sensitivity of 79.5% and a specificity of 90.2%, with a positive predictive value of 40.3% and a negative one of 98.1%. Thus, patients with a score greater than or equal to 4 points were considered "patients at risk for the development of AL".

This score was also correlated with length of hospital stay and mortality.

The 4th study, "Methods of Securing Sutures in Digestive Surgery," investigated the mechanical properties of the suture and anastomosis line secured with cyanoacrylate (CA) adhesives. This involved an experimental *ex vivo* study on the small intestine of ovine origin. Ten anastomoses and 20 sutures were performed and the physical properties were studied.

Higher mean values of fistulizing pressure and breaking strength were found in the group of anastomoses and sutures provided by application of cyanoacrylate (by 23.8% among anastomoses and by 36.7% in the case of sutures).

This study did not evaluate the biological effects of cyanoacrylates and did not compare the mechanical properties of other currently available classes of adhesives. Cytotoxic

effects, carcinogenicity and other potential adverse effects should be studied *in vivo* and remain an open subject for other studies.

If they prove their effectiveness and safety in use, cyanoacrylates will be a tool in the arsenal of modern digestive surgery aimed to increase the safety of the medical act.

The development of biotechnological branches, genetic engineering, the development of biomimetic technologies will probably lead to approve new compounds with indication in the prevention and therapy of digestive tract fistulas (acellular matrices or developed *in vitro* tissue fragments, reepithelization stimulating compounds, non-immunogenic adhesives).

The main conclusions of this paper are:

1. AL is a post-operative complication that occurs most frequently in days 5-6 postoperatively, consuming a lot of human and material resources, with an incidence of 6.6 - 8.6%.

2. AL has a multifactorial etiology, each factor having its own degree of involvement;

3. The main risk factors for unfavorable involvement in the occurrence of AL (from the studied list) were atherosclerotic disease, obesity, diabetes, hypocalcemia, hypertriglyceridemia, emergency interventions, occlusive syndrome, presence of peritonitis, heart failure, perioperative need for blood transfusions or administration of inotropic/vasopressor drugs, advanced stage of neoplastic disease, with the presence of secondary determinations;

4. The incidence of Al was not favored by sex, age, the presence of benign hepatic or renal pathologies, nor by the presence of neoplasms in non-metastatic stages;

5. The dramatic effects of AL make it necessary to develop tools (formulas) capable of identifying (preoperatively and accurately) patients at risk for AL development;

6. Identifying the patient at risk for AL involves actively seeking out potential risk factors and interpreting them as a whole;

7. The preoperative risk assessment system for fistulous complications designed and proposed for use (FISTULA SCORE) is a new tool for identification and quantification of the risk, with improved predictive values, but with a complex calculation formula, which can lead to low adherence and reduced practical use;

8. Cyanoacrylate type adhesives improve (*ex vivo*) the mechanical properties of digestive sutures and anastomoses and can be a tool in the medical arsenal meant to increase the safety of the patient.

Some results confirm the data published by other authors, but there are also contradictory ones. These differences may be due to the following issues:

(a) the descriptive studies were carried out in a single ward, in a single hospital in Bucharest;

(b) the department in which the analytical studies were performed is not one dedicated to digestive surgery but one to general surgery;

(c) studies in relatively small groups of patients;

(d) a small number of certain types of surgery (such as pancreatectomies, choledochal-enteral anastomoses, or choledochal-choledochal anastomoses) that cannot support the results of statistical analyzes;

(e) data taken from the patients' medical folders, which may result in unintentional transcription errors or incomplete data processing (incomplete history, incomplete diagnosis or coding errors);

(f) the absence of standard protocols for preoperative clinical and paraclinical evaluation of patients;

(g) the experimental studies were performed exclusively *ex vivo*;

These shortcomings lead to:

(a) the need for further multicenter studies in larger patient groups with a variety of pathologies;

(b) the need to identify other possible risk factors;

(c) applying FISTULA SCORE to larger groups of patients to study (confirm or refute) their predictive abilities and to determine the benefit of their use;

(d) developing new scores with good predictive values to identify patients at risk;

(e) the need for easy-to-use automated scoring programs (calculators);

(f) confirmation or refutation of the results on the efficacy of cyanoacrylate group adhesives on *in vivo* models;

(g) study of the short-, medium- and long-term biological effects of CA-type adhesives;

(h) study of other groups of adhesives or techniques with potentially beneficial effect in the prevention of fistulous complications.

Until the implementation of new techniques and devices able to eradicate this type of complication, with fatal potential, I consider patient safety above any surgical ambition and that the necessity of risk evaluation and adaptation of the surgical technique in every patient is a must.

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