Study Protocol + Statistical Analysis Plan (SAP)

ROLE OF O2 AVAILABILITY IN ANASTOMOTIC LEAKAGE IN LAPAROSCOPIC COLORECTAL SURGERY FOR CANCER

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Introduction

Colorectal cancer is the third most commonly diagnosed cancer in the world. It accounts for 11% of all cancer diagnoses, and is the fourth leading cause of cancer mortality, with 1.8 million new cases and approximately 861,000 deaths in 2018 (GLOBOCAN CHI database). Surgical resection is the mainstay of therapy for patients with non-metastatic disease, and has a significant impact on the long-term survival of patients with metastatic disease (3). Outcome is closely related to the quality of preoperative staging, surgery, and multidisciplinary patient management (4-5).

Anastomotic dehiscence (AD) is the most feared complication following resective colorectal surgery due to the high rate of morbidity and mortality that results from the worsening of the overall and oncological outcome of the patient and the increase in the time and costs of hospitalization (6). The International Study Group of Rectal Cancer has defined AD as "a communication between intra and extra luminal compartments due to a defect in the integrity of the intestinal wall at the anastomosis between intestinal segments" (7). In literature the mortality rate resulting from AD is very variable.

An Australian study of 1,598 patients recorded a mortality rate of 1.7% (8), but other case studies report a higher percentage, up to 29%. (9-10-11). Approximately 1/3 of deaths following colorectal surgery are attributable to this complication (12).

The incidence varies depending on the anatomical location of the anastomosis: 1--20% in the case of colorectal anastomosis; 0--2% in the case of colo--colic anastomosis and 0.02--4% in the case of ileo--colic anastomosis (13--14--15--16). Risk factors for anastomotic leakage can be divided into preoperative, intraoperative, and postoperative factors.

All can be traced back to two main groups: local, related to the surgical technique, and general, related to the patient. As regards local factors, the most significant are: experience of the surgeon (especially in the case of laparoscopic surgery), distance from the anal margin, suturing of the anastomosis using manual or mechanical staples, type of anastomosis (lateral--to--side, end--to--side, end--to--end), tension, vascularization and hemostasis of the anastomotic ends, presence of a protective stoma, placement of drains, bowel preparation, role of the microbiome (17). Review from 2015 identified several patient-related modifiable and non-modifiable risk factors, including: male sex, smoking, habits, alcohol consumption, obesity, diabetes, vascular disease, use of anti -inflammatory drugs, transfusions, hypoalbuminemia, anemia, intraoperative hypotension and use of cardio--vascular drugs, neoadjuvant radiotherapy and chemotherapy(18).

A factor that occurs in almost all these conditions is an alteration in tissue perfusion, and therefore in oxygen availability with consequent micro--ischemia of affected segments and failure of the anastomosis.

Reduced availability of oxygen, in addition to the patient's condition, which can affect it both pre- and post-operatively, can also occur intraoperatively. Good tissue oxygenation can favorably influence the outcome of anastomoses. One study in fact has documented a reduction in the risk of AD following colorectal and gastric surgery with the administration of supplemental oxygen alone (FiO_2 80%) during the procedure and for 6 hours thereafter (19).

However, the availability of O_2 is not determined exclusively by the inspiratory fraction of O_2, but by factors present in the equation that defines the Oxygen Availability (DO_2):

$$DO_2 = CO \times CaO_2, \text{ where } CaO_2 = (Hb \times SaO_2 \times 1{,}39) + (0{,}0031 \times PaO_2)$$

CO: Cardiac Output; CaO_2: Arterial Oxygen content

In this equation the portion of DO_2 attributable to the dissolved form of O_2 in arterial blood (PaO_2) is negligible. Therefore the following equation can be considered:

$$DO_2 = CO \times Hb \times SaO_2 \times 1{,}39$$

Considering all the parameters involved allows to have a more correct and complete idea of peripheral tissue perfusion. There is only one study in literature in which the indexed DO_2 (DO_2I) is put in relation to the incidence of AD (20). In this study the CO of 75 patients undergoing colonic resection was monitored via Doppler probe in the esophagus. The results show that patients with a DO2I <400 ml/min/m2 have a significantly higher risk of developing AD.

The use of the esophageal Doppler probe for monitoring cardiac dynamics is, however, highly invasive and cannot ignore the operator's experience. Furthermore, it requires frequent checks of the correct positioning of the probe itself. It also presents some, albeit rare, contraindications.

Currently, there are several methods for cardiovascular monitoring that allow obtaining sufficiently reliable hemodynamic data while being less or absent invasive and easy to interpret. Through non-invasive analysis of the shape of peripheral blood waveform (pulse--contouring volume--clamp technique) by inflating a cuff placed on the patient's finger, it is possible to obtain complete information about volume status and preload, cardiac function and afterload, in an easily usable format (21--22).

To calculate DO2I it is also necessary to know the patient's total hemoglobin (Hb) value, data obtainable with a blood test, normally performed preoperatively. However, during the surgical intervention, numerous factors contribute to modifying the Hb concentration, such as the patient's volume status and blood loss.

To obtain reliable intraoperative data, it would therefore be necessary to resort to serial blood sampling, venous or arterial which is clearly invasive for the patient and an expenditure of economic resources. Currently, there are new-generation pulse oximeters on the market that analyze different wavelengths and simultaneously measure multiple parameters: O2 saturation, heart rate, respiratory rate, total hemoglobin, carboxyhemoglobin, and methemoglobin, arterial O2 content, perfusion index, and plethysmographic variability index.

With this new technology it is therefore possible to obtain non-invasively and continuously more real and complete data, little influenced by patient movement and by conditions of low perfusion (23--24).

Aim of the study

To evaluate the effects of DO2I on the incidence of AD in patients undergoing laparoscopic resection for colorectal cancer.

Materials and Methods

Patients attending the General Surgery Unit of the S. Eugenio Hospital in Rome will be enrolled who meet the following inclusion criteria:

-age > 18 years

-candidates for laparoscopic colorectal surgery in elective for neoplastic pathology

Patients will be excluded if they meet the following criteria:

-age <18 years

-inability to express valid informed consent

-interventions that involve other areas of the body in addition to the colon and rectum

-emergency interventions

-open surgical interventions

-patients who have contraindications to the use of the volume--clamp system for hemodynamic monitoring (conditions that alter significantly the perfusion of the fingers, e.g. Raynaud's disease)

Each patient will follow a preoperative evaluation according to the clinical standards of the Anesthesia and Intensive Care Unit of the two recruiting centers: a complete physical examination will be conducted for all areas and a medical history aimed at identifying general and specific risk factors, and assigning a risk class of the American Society of Anesthesiologists (ASA).

During the preoperative period a blood sample will be take for a complete blood count coagulation tests, and chemistry tests.

All patients will be given a dedicated informed consent form which will explain the aims and methods of the study. Furthermore, all patients will be informed that the anesthesiological care is of equal intensity in each case, in accordance with the dictates of common and good clinical practice.

Patients will be subjected to general anesthesia (GA) with titrated doses of propofol 1%, fentanyl, rocuronium, desflurane, oxygen, and air, with complete noninvasive monitoring.
All enrolled patients will also be provided with non-invasive hemodynamic monitoring for the calculation of CO based on pulse-contouring type volume clamp, via the ClearSight system (Edwards Lifescience Corporation--USA). Non-invasive monitoring will also be applied for oxygen calculation using pulse oximetry sensors Masimo rainbow (Masimo Corporation – Irvine, California). The DO2I will be calculated at three moments and periods during the procedure: 5 minutes after the induction of GA, 30 minutes after the induction of pneumoperitoneum, 5 minutes after the end of pneumoperitoneum. This is intended to record the variation in DO2I in relation to the hemodynamic changes induced by pneumoperitoneum.
All patients enrolled will constitute Group A. Based on the average of three measurements of DO2I obtained during the intervention, patients in Group A will be distributed into three subgroups: DO2I <400 ml/min/m2 (Group A1), DO2I 400--600 ml/min/m2 (Group A2), DO2I >600 ml/min/m2 (Group A3). The values of DO2I chosen as cut-offs for the formation of the three subgroups were established by analyzing the studies by Levy and by Shoemaker (20--25).
For each of the three subgroups the incidence of AD will be calculated, also in relation to anamnestic risk factors.

Statistical Analysis

The data will be analyzed using the IBM SPSS software package (Armonk, NY), with calculation of medians and standard errors. For continuous variables, the t-test and ANOVA will be used. For categorical variables, the Fisher's exact test will be used. A p value < 0.05 will be considered statistically significant.

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