Absolok Hemostatic Evaluation In Colorectal Surgery

Version 1.1 – 28th of February 2022

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Synopsis

Overview and study rationale

Perioperative bleeding currently represents one of the most fearful complications in colorectal surgery, with a reported incidence rate ranging between 1% and 14%. The onset of perioperative bleeding may potentially lead to additional related adverse events, such as post-operative ileus, anastomotic leakage, and sepsis. This inevitably reflects in a prolonged length of hospital stay and higher costs for hospitalization.

In this context, surgeons' ability and the use of adequate hemostatic devices are fundamental to reduce the incidence rate of perioperative bleeding. In this regard, metallic clips are currently recognized as the most used devices for an appropriate ligation of vessels. However, episodes of clip migration and infection nidus formation have been reported in the literature. This has led to themore recent introduction of no-metallic clips, as a valuable alternative to the metallic ones. Amongthem, the Hem-o-lok and Absolok clips are recognized as the most frequently employed. Hem-o-lokclips are composed by no-absorble polymers, while the Absolok ones are characterized by bio- absorbable polymers.

Currently no comparative study is present in the literature between the Absolok and Hem-o-lok clips in terms of perioperative bleeding in colorectal surgery. Aim of this monocentric randomized open-label pilot clinical trial is, thus, to compare the hemostatic capability of these two devices in colorectal surgery.

Type of study

Monocentric randomized open-label pilot clinical trial.

Aims of the study

All patients candidate to colorectal surgical procedures (namely, right hemicolectomy, left hemicolectomy and rectal resection) will be enrolled in the study on the base of specific inclusion and exclusion criteria.

Primary aim of the study will be to evaluate the perioperative bleeding incidence rate between Hem-o-lok and Absolok clips according to the Spiegel bleeding grading scale.

Secondary aim will be a further comparison between the two devices in terms of intra- and post-operative course.

Security/adverse event management:

-All adverse events observed during the study will be collected and recorded. Adverse events involving medical devices and which qualify as incidents or deficiency will be reported to the National Competent Authority and to the Manufacturer in accordance with the provisions of current legislation for medical devices (EU Regulation 745/2017 and Legislative Decree 5 August 2022, n.137 and subsequent communications from the Ministry of Health).
Safety reference document: Instructions for Use and Technical Data sheet of the medical device(s) used in the study.

Introduction

Intraoperative hemorrhage is a recognized complication in colorectal surgery. Bleeding can be significant and difficult to manage, as conventional methods of haemostasis may prove inadequate. Severe cases that cannot be rapidly controlled may result in patient fatality (1). Appropriate preoperative planning, a meticulous and consistent surgical technique and the appropriate utilization of haemostatic adjuncts and devices are potentially useful strategies to minimize the risk of severe blood loss. In addition, the loss of normal tissue planes secondary to local tumour spread, irradiation and previous surgery can distort the normal anatomy, rendering dissection more complex(2,3). The

challenging anatomy is further complicated by the vasodilatory properties of anaesthetic drugs and the lithotomy position frequently utilized in colorectal surgery, resulting venous pooling and increased hydrostatic pressure, exacerbating blood loss (4,5).

Similarly, postoperative bleeding represents an additional serious complication after colorectal surgery, with an incidence rate. comprised between 1% and 14% of all colorectal procedures (6–8). Although postoperative bleeding is rarely fatal by itself, it is often the beginning of a cascade of serious com- plications, including ileus and anastomotic leak, which carry significant morbidity and mortality. Furthermore, therapeutic transfusions are also not benign and may result in transfusion-related acute lung injury, circulatory overload, immunosuppression, infection, and more (9,10). Transfusions and related complications prolong hospitalizations, adding an additional 2.5 days to the average duration of stay and $17,000 to the average cost of stay (11,12).

In this context, the surgeons' ability to achieve hemostasis is fundamental. Metallic surgical clips are widely used for this, but have disadvantages including a propensity to displace or act as a nidus for infection. This led to the more recent introduction of no-metallic clips. Among these last absorbable clips have been introduced as an alternative to the metallic ones. These clips are constructed from bio-absorbable polymers that degrade by hydrolysis over a period of approximately 6-7 months (13). Beyond this time, no foreign body exists to act as a nidus for infection. Previous microscopic analysis suggests that although the integrity of the clip reduces by 1week, vessels attain independent security by 24 h after clip placement, and there is a wide safety margin with regard to failure of ligation (14). Clips are certified for use with any general or surgicalligation need, including vascular and cystic duct ligation.

Currently, the two most widely available no-metallic products, are the Hem-o-lok® and the Absolok clip®.

Hem-o-lok® clips are composed by a non-absorbable, inert, non-conductive and radiolucent polymer that has no interference during X-ray, computed tomography (cT) or magnetic resonance imaging (Mri) diagnostics. Hem-o-lock clips have a lock engagement feature, as well as theeth in the jaws that provide good security. Although the use of Hem-olok® clips in closeness to the upper collecting system was traditionally considered safe, a few cases of complications due to clip migration into were reported (15–18).

Absolok clips are constructed from bio-absorbable polymers that degrade by hydrolysis over a period of approximately 6-7 months (13). Beyond this time, no foreign body exists to act as a nidusfor infection.They are characterized by a latch-closure mechanism.

Despite these premises, no comparative study between these two different type of no-metallic clips is currently present in the literature. Aim of this monocentric randomized open-label pilot clinical trial is thus to evaluate the safety of Absolok clips in terms of hemostasis as compared to the concurrent Hem- o-lok clips in colorectal surgical procedures. Secondary aims will be a further comparison between the two procedures also in terms of length of surgical procedure, intra-operative complications otherthan intraoperative bleeding and post-operative course.

Hypothesis and specific aims

This is a monocentric randomized open-label pilot clinical trial.

According to our hypothesis, Absolok clips would relate to a lower incidence of perioperative incidence of bleeding as compared to the Hem-o-lock ones. Consequently, the primary objective of our study will be the comparison between Absolok and Hem-o-lock in terms of hemostatic capability.

As further analysis, intraoperative data (namely operative time, intra-operative complications) and postoperative data (time to flatus, postoperative complications, length of hospital stay) will be compared between the two study cohorts. This analysis will be particularly focused on the potential clips-related complications.

Primary endpoint

The primary endpoint will be the percentage of subjects who achieve Grade 3 or lower hemostasis for each vessel clipped and transected, according to the grading scale (19) reported below:

- Grade 1: no bleeding at transection site;
- Grade 2: minor bleeding at transection site, no intervention needed;
- Grade 3: minor bleeding at transection site, mild intervention needed, use of compression, basic energy devices (monopolar and/or bipolar)
- Grade 4: significant bleeding (e.g., pulsatile blood flow, venous pooling) requiring intervention such as extensive coagulation or ligation with use of additional hemostatic measures (e.g., hemoclips, staples, sutures, fibrin sealants, other advanced energy products).

Secondary endpoint

The secondary endpoint of the study will be the evaluation of the potential influence of the type of clip employed on the intraoperative and postoperative courses. For this purpose, the following outcomes will be evaluated:

- operative time
- intra-operative complications
- time to flatus
- postoperative complications
- length of hospital stay

Patients' enrolment

Patient enrollment will take place at the Hospital Isola Tiberina – Gemelli Isola and will be based on the following inclusion and exclusion criteria.

Inclusion criteria:

- All patients undergoing curative colorectal resection for benign and malignant disease, here including right hemicolectomies, left hemicolectomies and rectal resections

Exclusion criteria:

- Patients aged < 18 years
- Inability to give informed consent
- Emergent surgery
- Previous colorectal surgery
- Uncontrollable diabetes mellitus that needs continuous intravenously administered insulin
- History of myocardial infarction or unstable angina pectoris within 6 months
- Cardiac failure, New York Heart Association (NYHA) III degree
- Anticoagulant therapy
- Liver cirrhosis, Child-Pugh class C
- Active hepatitis
- Chronic renal failure requiring hemodialysis

Statistical design

Sample size calculation

Currently, there is no comparative study between Absolok and Hem-o-lok clips in terms of perioperative bleeding in colorectal surgery. Therefore, this study is configured as a pilot study, such that a formal calculation of the sample size is not necessary. Thus, all patients undergoing colorectal surgery at the Ospedale Isola Tiberina – Gemelli Isola of Rome will be enrolled in the study. Enrollment will last 1 year (12 months) from the start date of the study. Eligible participants were randomized 1:1 to Absolok® or Hem-o-Lok® using a computer-generated allocation

sequence (PASS 2019) without stratification. According to mean number of colorectal resections performed during the previous two years, a totalnumber of almost 200 patients are expected to be enrolled.

Statistical analysis

All variables will be represented by descriptive statistics techniques. In depth, data will be reported as absolute and percentage frequencies, as for qualitative variables. Quantitative data distribution will be assessed using the Shapiro-Wilk test. Hence, data will be expressed either as mean ± standard deviation (SD) or median and interquartile range (IQR), as appropriate.

As for the primary endpoint, the difference between Absolok and Hem-o-lok in terms of achievement rate of Grade ≤3 hemostasis for each vessel clipped and transected (dichotomous variable) will be assessed by the Fisher exact test. The single grading scale will be further reported.

Between groups differences will be assessed by the Fisher exact test and the Chi-square test, with Yates correction, as appropriate, in the case of qualitative variables. Quantitative data, indeed, will be assessed either by the Student's t test or the non-parametric Mann Whitney U test, as appropriate.

As for the secondary endpoints, the potential association between the type of clip employed and the intraoperative and postoperative courses will be computed by using the same test, as aforementioned.

All analyses will be performed by using R software, version 4.1.2 (CRAN ®, R Core 2020).

Surgical design

All patients undergoing colorectal resections (namely, right hemicolectomies, left hemicolectomies and rectal resections) will be included in the study, independently of the type of approach to be performed (open, laparoscopic, robot-assisted) The following steps are required in all cases, independently of type of surgical clips used.

Right hemicolectomy

The ileocolic pedicle is identified by gently placing the ileocecal junction on stretch by pulling it away from the retroperitoneum towards the right lower quadrant. Once identified, the peritoneum of the mesentery just inferior to the vessel is opened using a cautery. The avascular plane between the mesocolon and retroperitoneum is then developed using blunt dissection to lift the vessel away from the retroperitoneum. The medial dissection of the ileocolic artery and vein is carried to its origin from the superior mesenteric vessels. Complete dissection in this bloodless plane is performed laterally over Gerota's fascia to the abdominal wall laterally and cranially over the duodenum and head of the pancreas entering the lesser sac. Toldt's fascia is carefully protected on the

retroperitoneum to protect the ureter and duodenum. Once the ileocolic vessels are isolated, they are divided between surgical clips (Hem-o-Lok® or Absolok®, according to the randomization). The right colic vessels have more variation and can branch from the middle colic artery or directly off the superior mesenteric artery and can also be transected by means of a Hem-o-Lok® or Absolok® clip, according to the group assignment. After completion of the vascular phase and adequate mobilization of the right colon, the greater omentum is divided, and the gastrocolic ligament is divided using an energy device (mostly ultrasound). The right branches of the middle colic vessels are then identified and divided with surgical clips (Hem-o-Lok® or Absolok®, according to group assignment). The terminal ileum is evaluated and divided at a site of healthy, well-perfused bowel. A linear cutting stapler is used to divide the bowel. The transverse colon is divided into a healthy and well-perfused area with a cutting stapler. Division of the mesentery and the resulting pulsatile bleeding can confirm good perfusion to the segment. The specimen is then removed from the field, and anastomosis is performed using a manual single-layer extramucosal isoperistaltic suture (open technique) or a semiautomatic mechanical isoperistaltic suture with a barbed monofilament to close the service enterotomy (laparoscopic–robotic intracorporeal technique). A Pfannestiel incision is routinely adopted for the latter cases to extract the specimen.

Left hemicolectomy

A medial to lateral approach is generally the preferred approach unless the surgeon is unable to safely identify the anatomy. This approach allows the surgeon to safely separate the left colonic mesentery from the retroperitoneum and protect the ureter, retroperitoneal blood vessels, and sympathetic nerves. The exposure is facilitated by reflecting the small bowel out of the pelvis using a lithotomic right lateral position of the table. Once the inferior mesenteric artery pedicle is placed on a gentle stretch, a mesenteric window is created with cautery. The pedicle is lifted upwards, and a gentle blunt dissection is performed in the proper congenital fusion plane between the Gerota and Told's fascias. Once the mesentery is lifted off, the retroperitoneum, left ureter and gonadal vessels are swept away from the pedicle. The inferior mesenteric artery is thus isolated and clipped by means of Hem-o-Lok® or Absolok® clips, according to the group assignment. The inferior mesenteric vein is then isolated and ligated by means of Hem-o-Lok® or Absolok® clips, according to the group assignment. The colon is further mobilized off the retroperitoneum by dissection through this thin peritoneal layer. The remainder of the descending colon is mobilized off the lateral retroperitoneal attachments, and the splenic flexure is routinely taken down to achieve a tension-free anastomosis. Typically, the lateral dissection continues, rolling the colon mesentery medially away from Gerota's fascia over the kidney. Renocolic, splenocolic, and phrenicocolic attachments are released, and a colo-epiploic separation is obtained using an energy device (mostly ultrasound). Finally, the

remaining peritoneal attachments are divided, taking care to protect both ureters and the sympathetic nerves at the sacral promontory. An energy device is used to thin out the rectal mesentery to prepare the rectum for transection after it is cut between clips (Hem-o-Lok® or Absolok®, according to the group assignment), and the superior rectal artery and vein running medially in the mesorectum. The rectum is transected with a linear cutter stapler, ideally in one single firing. A Pfannenstiel incision for extraction is preferred because of its lower risk of incisional hernia formation and wound complications in cases involving a laparoscopic-robotic approach. End-to-end anastomosis is performed according to the Knight–Griffen technique by means of a mechanical circular stapler.

Rectal resections

The same steps of the left hemicolectomy are adopted for rectal resections, and the dissection is extended over the extraperitoneal rectum. Intrapelvic dissection is carried out through standardized planes. Dissection of the rectum starts with an incision of the peritoneal fold in the pelvis. Mesorectal excision starts posteriorly by dissection through Heald's "holy plane"; it is carried on towards the lateral region of the rectum, sparing the lateral part of the lateral rectal ligaments, and extends on the anterior side in front of Denonvilliers' fascia. End-to-end anastomosis is performed according to the Knight–Griffen technique (Knight–Griffen results of double stapling by means of a mechanical circular stapler).

Risk analysis, possible problems and solutions

Since the surgical treatment will respect the International Guidelines, no additional risks areexpected

Safety/Adverse Event Management

All adverse events observed during the study will be collected and recorded.

Adverse events involving medical devices can be classified as incidents and deficiency, the aforementioned, as identified by the following definitions, will be reported to the National Competent Authority and to the Manufacturer according to the provisions of current legislation for medical devices (EU Regulation 745/ 2017 and Legislative Decree 5 August 2022, n.137 and subsequent communications from the Ministry of Health).

In the case of a medical device, it means for

• any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device.;

• any inadequacy in the identity, quality, durability, reliability, safety or performance of an

investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer;

• any incident, malfunction or alteration of the characteristics or performance of a device made available on the market, including the error of use caused by the ergonomic characteristics, as well as any inadequacy in the information provided by the manufacturer and any unwanted side effects.

A serious incident is defined as any incident which, directly or indirectly, has caused, may have caused or may cause one of the following consequences:

a) death of the patient, user or other person
b) serious deterioration, temporary or permanent impairment of the state of health of the patient, the user or another person;

c) a serious threat to public health

Significance and Innovation

If our hypothesis will be supported, Abosolok clips will be clinically confirmed as a more valuable device to reduce peri-operative bleeding incidence as compared to the Hem-o-lok clips.

Deliverable

The results will be presented in international conferences (EAES, SAGES, UEG) and aimed to be published on international and peer reviewed scientific journals (JAMA, Annals of Surgery, British Journal of Surgery, Surgical Endoscopy)

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