

Official title:

Polypectomy With Hot vs Cold Snare in Small Colonic Lesions

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Abstract

Colonoscopy is the technique of choice for the diagnosis and prevention of colorectal cancer (CRC). The identification and extirpation of adenomas decreases the incidence of CRC by up to 76%. More than 70% of the excised lesions are less than 10 mm. There is controversy about the technique to be used (resection with cold vs hot snare) in the lesions of 5-9mm. Both use a polypectomy snare, differing in that the cold handle cuts by friction, while the hot snare uses electrical current. We propose a multicentre randomized clinical trial comparing both endoscopic techniques. At least 394 injuries per group will be included, randomizing patients to whom a diagnostic colonoscopy is requested for symptoms, screening or revision protocols. Randomization will be performed stratified by endoscopist. The primary objective is the proportion of incomplete polypectomies, which will be analyzed centrally from random biopsies of the edges of the lesion. As secondary objectives, we will compare the proportion of immediate and delayed hemorrhagic complications, the evolution of postprocedural abdominal pain and the factors associated with incomplete excision in each group and the factors associated with a failed cold polypectomy. The analysis of the primary objective will be carried out by means of the z test of homogeneity without using the correction of Yates, estimating the confidence interval of the difference between both groups. The analysis will be carried out by intention to treat and by protocol.

1. Introduction

Colorectal cancer (CRC) is a major cause of morbidity and mortality worldwide. It is estimated that in 2008, 1233,000 new cases were diagnosed and more than 600,000 people died for this reason throughout the world (1). Colonoscopy is the technique of choice for both diagnosis and prevention (2), since the identification and removal of colonic adenomas reduces the incidence of CRC by up to 76% (3-7).

Different endoscopic techniques have been developed for the removal of adenomas; The choice of some over others is made according to the size, morphology and location of the lesion.

In lesions of 5-9 mm there is controversy about the relevance of using the hot or cold handle. Both techniques use the same instrument, a polypectomy loop, differing in the cut they make. In the cold snare the cut is produced by the friction of the metal snare on the mucosa, while in the hot snare, the passage of electrical current through the snare generates an increase in temperature that makes the cut. These differences condition that, although they use the same instrument, both techniques present significant differences in their execution.

The studies focused to compare endoscopic resection techniques focus on 3 main objectives: effectiveness (ability to completely remove the lesion), safety (presence of complications during the procedure or during follow-up) and associated symptomatology (duration and intensity of abdominal symptoms). after the colonoscopy). Currently there is few data available to evaluate the ideal technique in polyps of this size.

Regarding complications, in 2011 Paspatis et al published an essay comparing the cold snare (208 patients) with the hot snare (206) for the exeresis of polyps between 3 and 8 mm (8).

They focused on the immediate hemorrhagic complications, which were more frequent in the cold-snare group, but resolved spontaneously in all cases. The only study available that compares both techniques in polyps of 5-9 mm is a retrospective single-center study. a total of 148 injuries analyzed (9). They did not observe differences between the deferred complications between both groups (1.3% and 1.4%). Ichise et al published a randomized clinical trial evaluating abdominal symptoms after polypectomy, including 40 patients per group. The presence of abdominal symptoms (abdominal pain, diarrhea) in the two weeks following the examination was more frequent in the hot snare group (20% vs 2.5%) (10).

The evaluation of the resections can be done by several methods, which conditions the disparity observed in the different works. The ideal method would be the evaluation of the margins of lateral and vertical resection. However, this is complicated by the usual handling of the samples (fragmented samples, samples submitted for histological study in pot instead of mounted ...), so the number of non-valuable samples can reach 40% (11). Another option is to take biopsies from the edges of the lesion. Although it includes a component of subjectivity, depending on where the biopsies are taken, it allows to evaluate all the injuries. In 2010, Pohl et al published a paper based on data from 2 North American centers (12). All resections were made with hot loop, being incomplete in 6.8% of the lesions <10 mm. The cold loop technique presents similar results. In a study in which 59 slightly smaller polyps were analyzed (average size 3.7 mm), incomplete resections were observed in 6.8% (13). The studies in which the edges of resection are evaluated show greater proportions in both techniques. The work published in 2015 by Din and colleagues, comparing two techniques of cold cutting in lesions of 3-7 mm, observed a proportion of incomplete polypectomies close to 30% (14) while another retrospective observational work with 175 lesions of 3- 10 mm extirpated with cold snare and 1010 of 6-15 mm excised with hot snare, the proportion of histologically complete polypectomies was 53% and 61%, respectively (15).

2. Hypothesis

Conceptual hypothesis:

Cold snare polypectomy presents a proportion of incomplete polypectomies similar to polypectomy with hot snare.

Operational hypothesis:

Two endoscopic techniques will be compared from two groups created by a random assignment to one or another type of polypectomy, evaluating the proportion of non-excised polypoid tissue after it. This will be done from random biopsies of the edges of the lesion and possible macroscopic remnants

3. Objectives.

Primary objective:

To compare the proportion of incomplete polypectomies in both types of polypectomy (cold snare vs. hot snare).

Secondary objectives:

- ❑ Compare the proportion of immediate and delayed bleeding complications, total and according to the severity that they present according to the ASGE classification.
- ❑ Compare the evolution of abdominal pain in the 5 hours postprocedure between both groups.
- ❑ Evaluate the factors associated with an incomplete extirpation in each group.
- ❑ Evaluate the factors associated with a failed cold polypectomy.

4. Design

Randomized clinical trial comparing two endoscopic techniques.

5. Methods

Population to study

The study population includes patients scheduled to perform a colonoscopy in a non-urgent way. The patient will be invited to participate before performing the colonoscopy.

The variables defined in Annex 1 will be collected in a dissociated form database.

Inclusion and exclusion criteria

The inclusion criteria are:

- Patients older than 18 years scheduled to undergo a colonoscopy.

The exclusion criteria are:

- Absence of lesions of 5-9 mm.
- Contraindication for polypectomy (anticoagulant treatment, treatment with clopidogrel, coagulopathy or severe thrombocytopenia)
- Loss of polypectomy specimen
- Refusal to participate

Randomization

It will be done once the patient agrees to participate in the work and the first candidate polyp has been identified. Each patient will be randomized (regardless of the number of injuries per patient) in such a way that all lesions of each patient will be removed in the same way. It will be stratified by endoscopist, in such a way that each endoscopist will have its sequence of sealed randomization. Within each stratum a pure randomization will be carried out through a sequence generated by computer where the probability of belonging to each group will be 0.5. A total of 60 numbered sealed opaque envelopes will be available for each endoscopist that will be stored in the endoscopy room and will be opened consecutively as patients are included.

Intervention

Patients who meet the inclusion criteria and do not present any exclusion criteria (preendoscopic) will be invited to participate in the study. The informed consent will be completed according to the law 41/2002 of autonomy of the patient without it being altered the relationship with your doctor or any damage to your treatment.

1) Endoscopic act

The interventions will be carried out in each of the participating centers. The scans will be performed under sedation according to the protocols established in each center. Once the lesion is identified, the method of extirpation of the lesion will be randomized.

- Cold Group: polypectomy with a cold snare will be carried out according to the usual standards recommended by international societies. As far as possible we will try to arrange the lesion in the position equivalent to 5 o'clock on the dial, the end of the snare will be placed several millimeters from the lesion and the tip of the catheter will be angled downwards as the Asa, without aspiration at any time to avoid entrapment of the submucosa.

-Hot Group: polypectomy with snare connected to the electrosurgical unit according to the standards recommended by international societies, using a mixed current (cut-coagulation). Once the lesion is captured, the snare is pulled to slightly separate it from the surrounding mucosa before polypectomy. Elevation of the lesion prior to polypectomy will not be performed.

-Common evaluation: once the polypectomies are completed, the basis of the polypectomies will be evaluated, taking biopsies from any suggestive area and also 2 random biopsies at the base of the polypectomy.

2) Postendoscopic follow-up

After a minimum of 21 days and a maximum of 28 days from the endoscopic examination, the patient will be contacted by telephone to collect the form about the evolution of the abdominal symptoms and to collect data about the appearance of complications (questions will be asked about visits to the hospital and in a targeted manner about the most frequent symptoms of the usual complications (fever, hemorrhage, abdominal pain)).

3) Histological analysis

The analysis of the specimens of the polypectomies will be carried out in each center according to their usual protocol. The analysis of the biopsies of the base of the polyp will be carried out centrally by a pathologist with more than 5 years of experience in digestive pathology. Samples from the base of the polyp will be sent biweekly from each center to the university health care complex in Salamanca through a messenger service. The pathologist will be blinded regarding the histological diagnosis of the excised polyp and the type of polypectomy (although it is true that it is difficult to blind this last point since the presence of heat artifacts in those removed with a hot handle is very frequent). The samples sent for centralized analysis will not be conserved, but will be destroyed once the study is completed according to the usual protocols.

Sample size

Assuming a proportion of incomplete polypectomies in both groups of 10% (using the taking of biopsies as a diagnostic pattern) and setting an equivalence limit of 7%, a total of 315 lesions per group are estimated to have an α risk of 5% and a power of 80%. Assuming a proportion of losses (polyps not recovered for histological study, polypectomies of the failed Cold group of 20%), an estimated 394 lesions per group are needed, with a total of 788 lesions in total.

Data Collect

All the variables concerning the characteristics of the endoscopist, the patient and the injuries included will be collected in each center. The variables related to the histological diagnosis will be collected in the same way in the respective center. The variables concerning the follow-up will be collected in a centralized manner, through a telephone call that will be made between 3 and 4 weeks from the procedure. The variable related to the histological study of the base of the polyp will be collected in a centralized manner by the pathologist in charge of the analysis of the samples.

6. Data management

Data from the data collection notebooks will be merged by the main researcher or collaborating researchers anonymously, encrypted and dissociated from the clinical information by means of a patient identification code (ID), in a database made through the program Access (Microsoft Corporation, Redmond, WA USA). A copy of the database will be used in each participating center, which will be merged after completing the data collection. The responsible researcher will define an ID for each participant. The data entered in the

database will be anonymous and the database will be protected with a password to which only the researchers will have access.

The unified file will be kept at the Río Hortega University Hospital and will be maintained until the end of the study. Regarding the application of the Organic Law on Data Protection 15/1999 and Royal Decree 1720/2007 that develops it, it should be noted that the protocol defined in the project oriented to epidemiological analysis, determines that the files will record information completely anonymized

7. Statistical analysis

The Access program (Microsoft Corporation, Redmond, WA USA) will be used for the realization of the database and the statistical analysis of them will be carried out through the STATA program (StataCorp, 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). In the quantitative variables, the arithmetic mean and the standard deviation will be calculated (variables that do not follow a normal distribution according to the Kolmogorov-Smirnov test will be described with median, minimum, maximum and interquartile range), and the qualitative ones will be expressed as percentages and your 95% confidence intervals.

The analysis of the primary objective, the proportion of incomplete polypectomies in both groups will be compared by means of the z test of homogeneity without using the correction of Yates. The confidence interval of the difference between the two groups will also be estimated. The analysis will be carried out by intention to treat, regardless of the type of polypectomy performed and per protocol (assigning the lesions assigned to the group Cold that are extirpated with hot snare to the Hot group). To evaluate possible confounding factors (endoscopist, nurse, handle type, location ...), the STATA confound user command will be used, defining as a significant change that which conditions a change in the odds ratio greater than 10% with respect to the one obtained with the complete model. In case several models do not present differences greater than 10%, the most parsimonious will be chosen.

Within the secondary objectives, the proportion of complications in both groups will be verified by the de2 test. To evaluate the factors associated with incomplete polypectomies and those associated with failed cold polypectomy, multivariate logistic regression techniques will be used.

8. Ethical aspects

8.1 Benefit-risk assessment for research subjects

The present study involves the comparison of different endoscopic techniques for the resection of polyps. Both techniques are part of the usual clinical practice for the removal of

polyps between 5-9 mm, so participation in the study does not imply an increased risk of complications that would present the patient not participating in the study. The taking of biopsies, the only change from the usual clinical practice, has an extraordinarily low risk of hemorrhage ($<1/1000$), not presenting other associated complications. The only benefit will be observed in patients who document the persistence of adenomatous tissue at the base of the polypectomy, which would help to establish the follow-up intervals.

The participant will be identified in the study database by an identification code (ID). The databases and other documents of the study will be available to the Health Authorities if they consider it relevant, in no case will they be available to third parties.

The present study will not require an insurance policy for civil liability, covering any eventual damages or damages derived from it.

8.2 Confidentiality of the data

The data of the study will be initially dissociated from the identity of the participant, through an ID, by the responsible physician. The relationship between the ID and the identity of the participant will be guarded by the investigating doctors in a file protected with a personal password. The data will be entered into the database anonymously with the participant ID, to maintain its anonymity. The database will be protected by means of a password, and only accessible by researchers. During the study, strict compliance with Law 15/1999, of December 13, Protection of Personal Data is guaranteed.

9. Schedule and dissemination plan of the study

First year

Data Collection

Second year

Data analysis.

Development of tools for your application (online calculator, app).

Presentation at scientific meetings.

Publication of the results.