

Is the use of prophylactic hemoclips in the endoscopic resection of large pedunculated polyps useful? A prospective and randomized study

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Abbreviations: PPB, post-polypectomy bleeding

Background: The methods for preventing post-polypectomy bleeding (PPB) are not standardised and there are groups that use hemoclips for this purpose.

Objective: To study whether the use of hemoclips reduces PPB complications.

Materials and Methods: Prospective, randomised study of patients with pedunculated polyps larger than 10 mm. The patients were included in two groups (hemoclip before polypectomy -HC- and standard polypectomy -SP-). This study has been registered with the trial registration number NCT01565993.

Results: 105 polypectomies were performed (98 patients), 66 (62.9%) in the HC group. The total rate of complications was 10.6% in the HC group (4.5% early bleeding, 1.5% severe delayed bleeding, 4.5% mucosal burns, 1.5% perforation). In the SP group, the rate of total complications was 7.7%, (7.7% early bleeding, no significant differences). In view of the unexpected increase in the morbidity of the hemoclip group, the study was suspended without reaching the sample size. In an ad hoc analysis, which includes the standard polypectomy patients who refused to participate in the study (35 polyps), the total morbidity was 5.7% (no perforations and 2 patients with premature bleeding). When we compared the morbidity of the HC group to the morbidity of SP group plus R group (74 polyps), we also failed to detect any significant differences in terms of PPB, but did in terms of perforation.

Conclusion: The prophylactic use of hemoclips in polypectomies of large pedunculated polyps leads to a further risk of mucosal burns and perforation that is not acceptable, and does not reduce the risk of PPB.

Introduction

Endoscopic polypectomy is a non-standardized technique and is not exempt from risks. Its main complications are digestive bleeding and perforation. The risk factors for developing post-polypectomy bleeding have been studied,^{1,2} evidencing a greater risk for elderly patients suffering from, chronic renal insufficiency, cardiovascular comorbidity, anticoagulant treatment or polyps larger than 1 cm.

The immediate or delayed bleeding ranges from 0.3%-6.1%,³ which in some studies reaches 12%,⁴ increasing to 24% in polyps larger than 3 cm.⁵ Perforation is less frequent, with a rate of less than 1%.⁵

Premature bleeding is more frequent than delayed bleeding⁶ and is due to insufficient coagulation of the blood vessel in the

polyp's pedicle, which is sectioned during the polypectomy. Delayed bleeding can present up to three weeks after the intervention. The risk of bleeding in both cases varies based on the size and type of the polyps and their location. Specifically, the resection of polyps larger than 2 cm is associated with a greater risk of complications,⁷ mainly digestive bleeding.

In order to avoid post-polypectomy bleeding, various hemostatic techniques have been developed for prophylactic use,⁸ such as the endoloop, adrenaline injection and hemoclip.

The hemoclip has been used prior to performing the polypectomy on pedunculated polyps, applied to the stalk in order to obturate the feeder vessel.⁹ The hemoclip has also been used prophylactically, being placed immediately after resection^{10,11} although this use has been questioned since it does not reduce the risk of delayed bleeding.¹²

The aim of our study is to analyze the advantages of the prophylactic use of hemoclips before polypectomy in our usual clinical practice, through a prospective randomized study that determines their effectiveness compared to conventional polypectomy, assessing the decrease in immediate and delayed post-polypectomy bleeding.

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Materials and Methods

From 2007 to 2010, we performed a prospective and randomized study at our hospital which has 430 beds and is under the auspices of the Autonomous Community of Madrid's public health service, providing health care to a population of 250000 people.

This study was approved by the Hospital's Ethics and Research Committee in compliance with Good Clinical Practice guidelines and is endorsed by a national FISS research grant from the Spanish National Department of Health.

This study has been registered with the trial registration number (Clinicaltrials.gov identifier) NCT01565993 and has been presented according to the CONSORT Statement guidelines.¹³

The assumption we tested was whether the placement of prophylactic hemoclips on pedunculated polyps larger than 1cm reduces post-polypectomy complications (premature and delayed bleeding) compared to conventional polypectomies and are cost effective. As a secondary aim, we attempted to ascertain the feasibility of the hemoclippping procedure.

Enrollment

All of the consecutive patients aged over 18 years referred for colonoscopy to the endoscopy office were informed of the aims of the ongoing research and were invited to take part in the study for which they gave their informed consent before the endoscopic procedure was performed.

The patients were selected at the digestive endoscopy unit because they met the following inclusion criteria: they had one or more pedunculated polyps, the heads of which measured more than 1 cm (regardless of the stalk thickness and length), and they were compared against the size of the biopsy forceps (6 mm) and subsequently confirmed in the anatomical specimen; they did not have any hemostatic alterations at the time the endoscopy was performed (confirmed by the usual blood tests taken before the procedure). Patients undergoing anticoagulant treatment were included in whom anticoagulation had been suspended for the amount of time required in order to obtain a normal INR. Patients younger than 18 years of age or with a platelet count of less than 50000, INR larger than 1.5, or those who refused to give their informed consent, were excluded.

Randomization process

A computer-generated list of random numbers was used to assign the participants to two different study groups: group A (hemoclip placement before polypectomy) or group B (conventional polypectomy). Patients were allocated to either of the two branches of the study, according to the assigned number generated during the endoscopy using a random number generator for the first 400 patients, assuming that they met the inclusion criteria.

Where more than one polyp was observed in a patient, all the polyps were included in the same randomization group, so that they all underwent the same technique (conventional or modified polypectomy). In this respect, if they presented delayed bleeding, there was no doubt as to which polyp was the source of the bleeding and, therefore, which therapy had been used, since all the polyps had been treated using the same technique.

Conventional polypectomy was performed on the patients who refused to participate in the study, who received the same level of healthcare treatment as the others.

Three endoscopists participated in the study, which had 30, 12 and 6 years' experience, respectively. Due to the manner in which our department functions, the doctors which performed the procedure were not randomized.

Definitions

In order to test the ability of prophylactic hemoclippping to prevent post-polypectomy bleeding, we were required to register all the adverse events that occurred. These adverse events were called "complications", despite their severity and clinical significance. Therefore, verifying the rate of complications was the same as verifying the rate of adverse events, many of which were resolved at the endoscopy room, allowing patients to be discharged in the usual manner.

We define premature bleeding as the spurting or oozing of blood that occurs during the polypectomy procedure and does not stop immediately, which requires the use of a hemostatic technique to preventing making the situation worse. It is usually controlled during the performance of the test and does not modify the subsequent clinical management of the patient.

We consider delayed bleeding to be the bleeding that takes place hours after the polypectomy has been performed, which is clinically identified (outside gastrointestinal bleeding or instability of the patient), and subsequently confirmed by endoscopy.

We consider severe complications to exist whenever patients have hemodynamic instability, need to be transfused or admitted to hospital for further endoscopic treatment.

Endoscopic procedure

After written informed consent was obtained, the patients received conscious sedation with a combination of intravenous midazolam and meperidine. The procedures were performed using Fuji colonoscopes (Fujinon Corporation-Europe-GmbH Willich, Germany). Disposable electrosurgical snares (Olympus Medical Systems Corp. Hachioji-shi, Tokyo, Japan) and an electrosurgery unit ERBE (ERBE Elektromedizin GmbH, Germany) were used for polyp resection. In all the polypectomies that were assigned to group A, a rotatable clip-fixing device "Quickclip 2" standard was used (Olympus Medical Systems Corp. Hachioji-shi, Tokyo, Japan), with an opening diameter of 135° and a maximum insertion portion diameter of 2.6 mm.

When a pedunculated polyp was identified during the procedure and it was confirmed that it met the inclusion criteria, the patient was randomized. In group A, one or more clips (**Fig. 1**) were placed (based on the criteria of the endoscopist in accordance with the size of the pedicle), and the polyp was subsequently resected using a diathermy loop (**Fig. 2**). In group B, a conventional polypectomy was performed, which was not aided beforehand by any other hemostatic technique.

The patients that presented premature bleeding were treated with the usual hemostatic techniques (hemoclip, endoloop, argon, adrenaline injection), used as a monotherapy or in combination, required to stop the bleeding, in accordance with

the endoscopist's criteria. For the study, this adverse event was named and registered as a complication, irrespective of whether or not the endoscopist was capable of resolving the bleeding at the endoscopy room and the patient could be safely discharged. Also, between four and six weeks after the polypectomy, the patients were contacted by phone in order to confirm the absence of delayed bleeding and to determine whether or not they had been admitted to any other hospitals.

Statistical considerations

The rate of post-polypectomy bleeding reported in literature varies between 24%⁵ and the more usual rate of 3%-4%.³ Therefore, based on an anticipated decrease of at least 12% in the rate of adverse bleeding events between the group treated using hemoclips and the group treated using conventional methods, there was an alpha error of 0.05 and a statistical power of 80% (beta error of 0.2) with a patient inclusion rate of 1:1. The number of polyps required is 146 per group. Using the Fleiss correction, the final number is 164 per group.

A comparison between the two groups was based on the intention to treat principle. To study the differences between both groups, the statistical Student's t test was used for quantitative variables and the Fisher test for qualitative variables. The chi-squared test or the Mann-Whitney test were used for non-parametric data, adjusting for ties where necessary. P values smaller than 0.05 were considered statistically significant.

Protocol violations were identified and excluded from the analysis. All variables studied in this trial which were necessary to test the assumption and the secondary goal of the study were input into the database. All the complications that occurred throughout the span of the study were recorded.

All statistical analyses were conducted using the SPSS program version 11.0 for Windows and NR2IS macro (Bonillo, Doménech and Granero, 2003).

Results

Between 2007 and 2010 (period over which the study

was conducted), a total of 7897 colonoscopies and 2786 sigmoidoscopies were performed at our center, with an average of 220 polypectomies per year. We included 136 patients in the study between 2007 and 2010, in which 35 patients refused to participate. 101 patients were selected and randomized, 3 of which (2.8%) were excluded for failing to meet the inclusion criteria since they involved semi-pedunculated polyps measuring less than 1 cm.

Although the patients were randomized, the unit that must be taken into account in the study is the polyp. Therefore, various polyps from a single patient were included in the same group.

A total of 105 polypectomies were performed on 98 patients, 66 (62.9%) were included in the hemoclip group and 39 (37.1%) in the conventional polypectomy group. The basic demographic characteristics of both groups were uniform (Table 1).

In 10 of the 66 polyps (15.2%), the hemoclips were incorrectly placed, mainly because the pedicles were very thick and/or short. It was difficult to place the clip on the polyps with short pedicles, causing mucosal burns in three patients because the base of the polyp came into contact with the polypectomy snare and the hemoclip (Fig. 3).

The total complication rate was 10.6% (n=7) in the hemoclip group. If we provide a breakdown of the various complications, in 4.5% of the polyps (n=3) premature bleeding was observed that was controlled endoscopically without requiring hospital admission. One patient (1.5%), who had a polyp measuring more than 3 cm presented serious delayed bleeding which required a transfusion and admission to the ICU. Mucosal burns were identified in 4.5% of the patients (n=3), one of which presented delayed perforation (perforation rate, 1.5%) requiring surgical intervention and admission to the ICU. The rate of severe complications (including delayed bleeding and perforation) was 3% (n=2). In this hemoclip group, 71.4% (n=5) of the complications were resolved during the endoscopic procedure without any clinical consequences thereafter.

With respect to the conventional polypectomy group, the total complication rate was 7.7% (n=3), less than the hemoclip group, but this was not significant for statistical purposes compared to the hemoclip group. This complication rate was caused by premature bleeding. It involved three polyps in which immediate bleeding was identified after the polypectomy, which was controlled endoscopically without requiring admission.



Figure 1. Placement of hemoclips on the pedicle prior to the polypectomy

Table 1. Demographic variables and characteristics of the polyps in the two groups

Variable	HC group	SP group	p value
Age	64.05	65.55	0.431
Sex (male/female)	49/17	24/15	0.172
Comorbidity	26	18	0.921
Anticoagulation	2	6	0.177
Antiaggregation	8	8	0.279
Size of polyps			
>3 cm	6	1	0.234
2-3 cm	15	10	0.884
1-2 cm	45	28	0.474



Figure 2. Hemoclips on the pedicle after the polypectomy

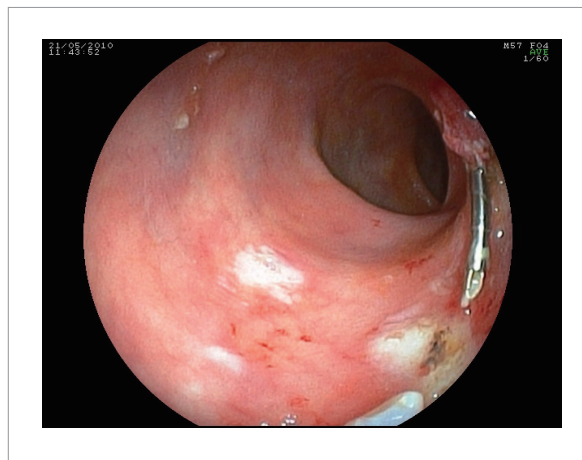


Figure 3. Mucosal burn following contact between the hemoclip and the diathermy loop and the base of the polyp

There were no cases of mucosal burns or severe complications (delayed bleeding or perforation).

The assumption on which the study was based was that post-polypectomy bleeding would decrease using the hemoclip procedure. However, in view of the unexpected increase in the morbidity of the hemoclip group in which serious complications arose during an interim analysis including delayed perforation following mucosal burns, the research team, in agreement with the Ethics and Research Committee, decided to discontinue the study. It became clear that based on the current results, it would be impossible to prove whether or not the assumptions tested were accurate. As a result, we failed to reach the sample size of 164 patients in each arm calculated initially, which explains the differences between the number of patients included in both groups.

We completed the assessment of the assumptions of the study using an ad hoc analysis, comparing the results of group A with the group of patients on which conventional polypectomies had been performed and who refused to participate in the study [R group (35 polyps)]. In this group, total morbidity was 5.7%, due to two polyps with premature bleeding, controlled endoscopically, without any differences that were statistically important compared to the hemoclip group. There were no data for delayed bleeding or perforation.

When we compared the morbidity of the hemoclip group with the conventional polypectomy group plus the R group (total of 74 polyps), we also failed to find any significant differences in terms of post-polypectomy bleeding, but we did with regard to perforation, which was not observed in any of the 74 conventional polypectomies (**Table 2**).

Discussions

Endoscopic polypectomy is a usual, non-standardized technique in clinical practice, because the electrical device used varies at the different endoscopy units because the power setting for the

different procedures can also be changed. This technique is not exempt from complications, mainly post-polypectomy bleeding. In order to avoid this complication, hemostatic procedures for prophylactic use were established, including endoloop, adrenaline injection or hemoclip.

A prospective randomized study published in 1996⁴ found that endoscopic resection with bleeding prophylaxis through endoloop placement is safer and more effective than conventional polypectomy, as it reduces the rate of bleeding in the endoscopic resection of pedunculated polyps larger than 2 cm. These conclusions were observed in subsequent retrospective studies.¹⁴ However, the use of the endoloop could pose greater technical difficulties due to transection by the loop of a thin stalk before the polypectomy or insufficient tightening of the loop.¹⁵ Moreover, we must remember that there are difficulties in looping big polyps with the endoloop and in the ultimate subsequent snaring of the polyp.

A randomized trial of prophylactic epinephrine-saline injection before snare polypectomy to prevent bleeding, did not find delayed post-polypectomy bleeding in either group.¹⁶ With regard to adrenaline injection compared to endoloop and hemoclip a prospective study,³ has shown that there are no differences between both techniques in post-polypectomy bleeding prophylaxis, although the combination of both procedures appears to be more efficient.¹⁷

Several studies compared detachable snare versus epinephrine injection, reporting no difference in delayed post-polypectomy and similar efficacy either by placing endoloops or by injecting epinephrine.¹⁸ Nonetheless, the use of adrenaline injection in combination with detachable snare may significantly decrease the number of early post-polypectomy bleeding episodes, in patients with large colonic polyps.¹⁹

There is a retrospective study⁹ that endorse the use of hemoclips because their prophylactic use is associated with a low risk of bleeding following the endoscopic resection of large pedunculated polyps. However, a recent article²⁰ submitted as

Table 2. Summary of complications and endoscopic therapy required in the three groups and in the final group resulting from the inclusion of the polypectomy group-patients that refused to participate. P value>0.05 in all cases

Variable	HC group	SP group	R group	SP+R group
n (polyps)	66	39	35	74
Early bleeding	3 (4.5%)	3 (7.7%)	2 (5.7%)	5 (6.8%)
Endoscopic control	3 (100%)	3 (100%)	2 (100%)	5 (100%)
Clip		1	1	2
Sclerosis	1	1	0	1
Sclerosis and clip	1	1	1	2
Sclerosis and argon	1	0	0	0
Delayed bleeding	1 (1.5%)	0	0	0
Mucosal burn	3 (4.5%)	0	0	0
Perforation	1 (1.5%)	0	0	0
Total of complications	7 (10.6%)	3 (7.7%)	2 (5.7%)	5 (6.8%)

an abstract to DDW 2011 (Digestive Disease Week), comparing the use of the endoloop to the hemoclip (prospective randomized study) concludes that there are no differences in both techniques in terms of effectiveness and safety. However, the contact between the loop with the clip if placed closed to the base of the pedicle can cause mucosal burns, increasing the possibility of perforation.⁹

To prevent this complication, hemoclips were used on the residual pedicle after the polypectomy^{11,12} a use defined as prophylactic given that it is placed before any bleeding is determined. However, this variation with regard to the placement of hemoclips is not simple, because the pedicle tends to retract after the polyp is resected. Accordingly, Mizukami's group¹⁰ developed a device ("Anchor clip") which, placed before the resection, constrains the base of the pedicle after the polypectomy, facilitating hemostasis and avoiding complications such as mucosal burns.

Theoretically, the placement of a prophylactic hemoclip to avoid premature and delayed post-polypectomy bleeding could seem attractive, safe and cost effective. In fact, there is a tendency towards its use at many endoscopy units. Hemoclips seem easier to place than the endoloop device and are more consistent than the adrenaline injection in order to prevent bleeding.

We have tried to test how useful prophylactic hemoclippping might be in order to prevent bleeding adverse events. Therefore, we need to register them irrespective of their clinical relevance and ultimate severity. The majority were resolved during the same procedure. If the hemoclip device had been useful in preventing bleeding, the rate of any adverse events in this group would have been very small, irrespective of the outcome of these bleeding episodes.

Our prospective randomized study comparing the use of prophylactic hemoclips prior to resection, to conventional polypectomy does not show any differences between both techniques. Based on the results of the interim analysis, we would have been unable to prove the assumptions of the study if we had continued recruiting patients. However, it establishes an unacceptable risk of mucosal burns and perforation that are associated with the use of the clips. Therefore, we were obliged to discontinue the study and conclude that the use of prophylactic hemoclippping to prevent post-polypectomy bleeding

is unsuccessful, is not cost effective and adds considerable risks of delayed perforation.

Most post-polypectomy bleeding was not clinically severe because the usual criteria of the endoscopist in this situation, is not to just wait and see. On the contrary, the normal procedure adopted is to try to stop the bleeding as soon as possible.

The patient who presented severe delayed bleeding had a big polyp measuring more than 3 cm. The size is an important risk factor of bleeding. The resection of polyps larger than 2 cm is associated with a greater risk of complications,⁷ mainly digestive bleeding. The endoscopist who carried out the polypectomy, had 30 years' experience.

The rate of complications during our study seems higher than that reported in literature, but most of these episodes were adverse events that were resolved at the endoscopy room that would not have been reported as a complication. The rate of severe complications did not differ from that published in literature.

The endoscopist's experience is a considerable factor in polypectomy. However, in this study the severe complications happened in polypectomies carried out by an endoscopist with wide experience (12 and 30 years experience). In these cases other characteristics as size of polyp and pedicle were important in the perforation and severe delayed bleeding.

With regard to the limitations of our work, since we did not reach the sample size established previously in the initial design, this implies bias and decreases the strength of the study. We think that based on the number of patients included before the research was discontinued, the study was able to show that the hypothesis tested was incorrect, and perhaps it contributed a new set of dangerous complications which were not previously taken into consideration.

Compared with studies that endorse the safety of the prophylactic placement of the hemoclip,²¹ in our study we had difficulties with regard to placing them and there was an inherent risk of bleeding and mucosal burns. On analyzing these complications, we discovered that the difficulty in placing the hemoclip was caused by polyps that had a thick or short pedicle. A thick pedicle made it impossible to place it completely, requiring more than one clip to be used, based on the criteria of the endoscopist. A short pedicle made it easier for the hemoclip to make contact with the base of the polyp, which led to mucosal

burns and, therefore, a risk of perforation.

These circumstances were identified during the compilation of data and the performance of the polypectomies and did not form part of the initial study objective of the work. Consequently, the variables included did not include the size or thickness of the pedicle and the characteristics of the pedicle were only described for the polyps in which the aforementioned difficulties were observed. Probably a selection of polyps with a long and thin pedicle might benefit from the use of prophylactic hemoclips, which could be determined by performing a sub-analysis of the length of the pedicle, a variable that was not included initially.

We therefore recommend that they be used in an appropriate location in the case of polyps with long and thin pedicles. In these polyps, the use of hemoclips prior to the polypectomy, do not make it difficult to perform the resection or increase the risk of complications.

Conclusion

The prophylactic use of hemoclips in polypectomies of large pedunculated polyps does not reduce the risk of post-polypectomy bleeding and also involves an unacceptable risk of mucosal burns and perforation.

Disclosure

The authors have no financial disclosures to make regarding potential conflict of interest.

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