Reviewer #1: Minor comments:

1-The authors excluded flat polyps that need different technical procedures and would increase the AEs rate and so it may be valuable to change the article title to " THE RATE OF ADVERSE EVENTS OF GASTRODUODENAL SNARE POLYPECTOMY FOR NON-FLAT POLYPS IS LOW: A PROSPECTIVE AND MULTICENTER STUDY" Would the authors agree?

We thank the reviewer for this observation. The title has been change.

2- Some minor typing errors e.g. "H. pylori" in the introduction to be italic " H. pylori"

Again, we thank the reviewer for the observation. H. pylori has been change by *H. pylori* in the introduction.

3- What sedations used among the patients? It was the same in all centers (standardized)?

Sedation was not standardized and was different in each hospital. Combinations were the following: Propofol, Propofol/Midazolam, Propofol + Remifentanil, Midazolam or Midazolam/Fentanyl (performed according to the endoscopist or anesthesiologist's preferences). This point has been clarified in Patients and Methods section (page 13).

4- AEs were assessed in this study and recorded by a physician. It is not clear whether he is one of the authors or an independent physician? Is he a gastroenterologist aware about the definition of AEs reported in the study? If no this may affect the incidence of AEs reported in the study?

All hospitals had a gastroenterologist responsible for collecting the data and they knew the definition of AEs. Then, database templates were sent to the national coordinator of the study (Dr. Córdova).

5-In this study most of the patients endoscoped were cold cases (only 33 patients endoscoped for upper GI hemorrhage) and there were 20 patients with cirrhosis, 36 on anti-coagulant therapy. Would the authors found it of value to check and correct coagulopathy among cirrhotics and stop anticoagulants (whenever possible) in advance as a prophylactic measure for bleeding among patients exposed to snare polypectomy?

Blood tests were only mandatory in patients with anticoagulation therapy or with conditions associated with coagulation disturbances (as cirrhosis). Patients with cirrhosis and a prothrombin time <50% or INR > 1.5 and platelet count <50,000 were excluded (as stated in the exclusion criteria).

Reviewer #2

Methods. 1-section 2.1: "Inclusion criteria were: 1) protruded gastric or duodenal polyps ≥5 mm and 2) polypectomy performed using an electrocautery snare". So when were the patients enrolled in the study? Before or after polypectomy? Were the patients consented for this prospective study? (They were consented for the procedure, but what about consent to be involved in the study?). It is unclear to me how patients were recruited. 2-in prospective studies, there should be a description of how many patients were evaluated and how many agreed to participate, how many met the exclusion criteria, and how many ended up being recruited. When were the patients told that they are part of a prospective study and that they will be contacted for follow up? Or were the patients not informed that they are part of a prospective assessment? When was IRB obtained? Before January 2012? Please submit a copy of the IRB (not just the statement)..I am afraid that the description of the study is actually describing prospective collection of data, and then the study idea was completed and IRB submitted after collection of data, this makes it a retrospective study, not prospective.

The reviewer is right with regards to the recruitment: patients were informed about the possibility of being included in the case they had a gastric polyp and underwent a polypectomy during the exploration and nobody refused tho participate. However, because the inclusion criteria stated a precise size, we gave the informed consent only to the patients who underwent the polypectomy and, therefore, it was after the exploration. Of the 326 patients included, 18 were excluded because of the violation of the inclusion criteria.

We consider the study prospective because we started the inclusion after writing a specific protocol and having the authorization of the IRB. Exactly, the preparation of the study began in January 2012 (drafting protocol, information and acceptance of other hospitals, etc.), IRB approval was obtained on July 26, 2012 (we submit a copy) and the first patient was included on September 21, 2012 (we submit a copy). The date has been corrected.

3.-The exclusion criteria: these are contraindications of polypectomy in general, but were there any patients who underwent polypectomy who were not

included in the study? or not followed? this should be clear in a flow chart diagram..

As mentioned before, 18 patients were excluded because of the violation of the inclusion criteria. Causes of exclusion are explained in the flow chart.

4-did any trainees participate in the polypectomies across these 15 hospitals? in table 5 there are 40 trainees? This should be mentioned in table 2.

We thank the reviewer for this observation. This information is now displayed in table 2.

5-gastroduodenal polypectomy in the title and in the aims section should specify that this study addresses polypectomy of protruded lesions (sessile or pedunculated) and not flat. therefore in title should be " the adverse event of polypectomy of protruded gastroduodenal lesions is low " or something similar.

Again, we thank the reviewer for the observation. The title has been change (THE RATE OF ADVERSE EVENTS OF GASTRODUODENAL SNARE POLYPECTOMY FOR NON-FLAT POLYPS IS LOW: A PROSPECTIVE AND MULTICENTER STUDY).

6-section 2.6. Sample size calculation is unclear. Why did you need specifically 30 AE?

Sample size calculation was performed, assuming 10% of AE from the previous data published. With these numbers, we calculated that a total of 300 patients were required to achieve statistical significance (α error = 0.05, β error = 0.1). A new paragraph and references has been added.

**SAMPLE SIZE & POWER DETERMINATION: One single proportion**

Proportion (%) of events in: Reference Population= 10%
Proportion (%) of events in: Sample= 5%
Minimun expected effect size: Difference= -5%

| | | SAMPLE SIZE | | | | | |
|---|---|---|---|---|---|---|---|
| Alpha Risk=5% | | Two-Sided Test | | | One-Sided Test | | |
| METHOD | Power | 80% | 85% | 90% | 80% | 85% | 90% |
| Normal* | n | **239** | **265** | **301** | **184** | **207** | **239** |
| Normal corrected | n | **279** | **305** | **341** | **224** | **247** | **279** |
| ArcoSinus | n | **212** | **243** | **284** | **167** | **195** | **232** |

(*)WARNING: Applicability conditions for Normal method not granted
N*P, N*(1-P), N*P1 and N*(1-P1) must be >=10
P and P1 must be >=20 and <=80

7-table 1 : anticoagulation: were these patients on anticoagulation that was stopped before the procedure? What about after the procedure?

3 days before the procedure, oral anticoagulants was replaced by subcutaneous low-molecular weight heparin. The patients were guided to reintroduce the oral anticoagulants 24-h after the procedure (the anticoagulant dose depended on the value of the INR value before the polypectomy). This information has been added as a new paragraph in the section of patients and methods (page 13).

8-table 1 : an patients on antiplatelet therapy that was resumed after the procedure? (methods -exclusion criteria --asa or Plavix before the procedure, but were any patients enrolled who resumed these medications after polypectomy? when did they resume it?)

The same day after the procedure, intake ASA or Plavix at usual doses was resumed.

9- in the prophylactic measures, APC is mentioned, how is APC used to prevent bleeding? please describe the technique.

Argon plasma coagulation was applied in the postpolypectomy scar of sessile polyps > 20 mm in cases of oozing bleeding with spontaneous hemostasis in less than 30 seconds (as stated in the paragraph of bleeding prophylaxis) (page 15).

10-the association of factors with bleeding is poorly described. For example in the statistical section the authors mention "a multivariate logistic regression analysis was carried out to assess the existence of predictive factors of AEs and the odds ratio (OR) was calculated to indicate the associated risk." where are these Odds ratios in the study? What were the model selection criteria and what variables are in the final model? Table 5 only includes univariate analysis, and since the AE are low, it is hard to have a meaningful analysis to associate risk factors with bleeding.

We agree with the reviewer that the number of AEs is very low and this has been mentioned as a limitation of the study. For this reason, we decided to perform an analysis of the predictive factors of any episode of post-polypectomy bleeding (n=30).

For the multivariate analysis we included variables with statistical signification in the univariate (size and explorer) and those considered clinically relevant.The variables in the final model were: size, anticoagulation, endoscopist expertise, prophylactic measure, endocut, hyperplastic type polyps, Paris classification polyp. These variables are marked with an asterisk in the

new version. Because the multivariate analysis did not show any significant variable, we did not show any OR.

Logistic regression — Number of obs = 271; LR chi2(6) = 11.45; Prob > chi2 = 0.0754; Log likelihood = −90.641084; Pseudo R2 = 0.0594

| Bleeding | Odds Ratio | Std. Err. | z | P>\|z\| | [95% Conf. | Interval] |
|---|---|---|---|---|---|---|
| size | 1.675023 | .8129873 | 1.06 | 0.288 | .6469675 | 4.336696 |
| endoscopist | 1 | (omitted) | | | | |
| hiperplastic | .474662 | .196107 | −1.80 | 0.071 | .2112077 | 1.066741 |
| endocut | 4.354111 | 3.385542 | 1.89 | 0.058 | .9485216 | 19.98719 |
| anticoagulation | 1.650347 | .6763186 | 1.22 | 0.222 | .7391793 | 3.68469 |
| prophylaxis | 1.063686 | .5002014 | 0.13 | 0.896 | .4231883 | 2.673582 |
| paris | .6748607 | .2342455 | −1.13 | 0.257 | .3417909 | 1.332502 |
| _cons | .0231765 | .0277805 | −3.14 | 0.002 | .0022119 | .2428508 |

. logit ComplicHemorragia tamaÒo explorador Hiperplasino endocut antiagreanticoa medidaprofil·ctica clasParÌs, or

note: explorador != 0 predicts failure perfectly

explorador dropped and 38 obs not used

Iteration 0: log likelihood = -96.367256

Iteration 1: log likelihood = -91.072104

Iteration 2: log likelihood = -90.643394

Iteration 3: log likelihood = -90.641085

Iteration 4: log likelihood = -90.641084

Logistic regression Number of obs = 271

LR chi2(6) = 11.45

Prob > chi2 = 0.0754

Log likelihood = -90.641084 Pseudo R2 = 0.0594

---

Bleeding | Odds Ratio Std. Err. z P>|z| [95% Conf. Interval]

---+---

| | | | | | | |
|---|---|---|---|---|---|---|
| size | 1.675023 | .8129873 | 1.06 | 0.288 | .6469675 | 4.33669 |
| endoscopist | 1 | (omitted) | | | | |
| hiperplastic | .474662 | .196107 | -1.80 | 0.071 | .2112077 | 1.066741 |
| endocut | 4.354111 | 3.385542 | 1.89 | 0.058 | .9485216 | 19.98719 |
| antiacoagulation | 1.650347 | .6763186 | 1.22 | 0.222 | .7391793 | 3.68469 |
| profphylaxis | 1.063686 | .5002014 | 0.13 | 0.896 | .4231883 | 2.673582 |
| paris | .6748607 | .2342455 | -1.13 | 0.257 | .3417909 | 1.332502 |
| _cons | .0231765 | .0277805 | -3.14 | 0.002 | .0022119 | .2428508 |

11- Around 70% of patients received prophylaxis, while only 15% of polyps were >=20mm which was the criteria for prophylaxis. Does that mean that the rest of the polypectomies received prophylaxis because of oozing or visible vessel? Please elaborate on why so many patients received prophylaxis for bleeding. In clinical practice most patients with polyps <20mm do not need any prophylaxis.

Prophylaxis criteria were very strict and included a stalk > 5 mm.

Reviewer #3: This manuscript reports the results of studies on the rate of adverse events associated with gastric and duodenal endoscopic polypectomies using hot snare procedure. Based on the data obtained with 308 patients, the rate of adverse events (mainly bleeding) appears very small. Hence, the procedure appears to be safe and effective. This paper is written, and the results are presented and discussed within the available literature on the subject.
We thank the very good reviewer's comment.

Reviewer #4: This paper includes the results of a multicenter prospective study of the gastric polypectomy risks found in a large series of patients The study is very well designed and performed The are few bleeding complications after the polypectomy and the patient ´s evolution was good There are few studies about this subject

We thank the very good reviewer's comment.