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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 26186
Title: PROSPECTIVE EVALUATION OF A NEW DEVICE FOR THE TREATMENT OF ANAL FISTULAS
Reviewer's code: 02411089
Reviewer's country: Turkey
Science editor: Jing Yu
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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	GoogleSearch:	[ ] Accept
[ ] Grade B: Very good	[Y] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[Y] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ]Plagiarism	[Y] Minor revision
[ ] Grade E: Poor		[ ] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ]Plagiarism	
		[ ] No	

COMMENTS TO AUTHORS

1) Authors declare "no conflict of interest" but what was the financial funding of the study material?

Answer: this plug is commercially available in Europe, since the producer obtained the CE mark; our Hospital simply bought the plugs.

2) Postoperative seven days use of antibiotics is not a common practice. This is not prophylaxis. Is this their routine for any type of fistula surgery? If so, I'd doubt about authors' level of experience, if not why did they choose such a regimen in this study.

Answer: postoperative use of the antibiotics is not our routine regimen in the treatment of anal fistulas. This study represents our early experience with the use of this specific device, so we decided to have some extra-precautions as the post-operative use of antibiotics,or as the discharge of the patient after 1 night stay. The absence of major postoperative complications (included sepsis)

probably has shown that our regimen treatment was not wrong. Given this, we think that a safe implant of the device without postoperative antibiotics administration could be evaluated in a future study.

3) How did they decide "absence of abscess"? EAUS is not sufficient to evaluate the absence of abscess and presence of fibrosis as a marker of healing of the fistula. Why did they not use MRI? MRIs of the study patients might provide a better understanding of the efficacy of the procedure. Maybe they can call the patients and study MRI of the anal region.

Answer: at our institution we routinely use the 3D-EAUS in the management of anal fistula patients (Dis Colon Rectum. 2000;43:1375-82; Endoscopy. 2005;37:722-8). As known, it is a powerful, cheap, easy and rapid instrument to accurately evaluate the acute (abscess) and chronic (fistula) phases of the perianal sepsis. In this preliminary study we did an EAUS at the every FU visit to assess the fistula healing process by evaluating the absence of an internal abscess (for example, an intersphincteric abscess would not be evident at a simple visual inspection), and the absence of the persistence of inflammatory tissue around the fistula tract. This was done to avoid considering as healed a fistula simply when the external opening was closed, not considering the possibility of a "quiescent" internal fistula. It is very well assessed in the Literature that a failure (persistence/recurrence) of the fistula treatment is evident at the EAUS as a hypoechoic image (granulation tissue, pus), while a healed fistula appears like a hyperechoic image (fibrosis, scar) in the area of the previous fistula (Dig Liver Dis 2006;38:537–43; Colorectal Dis 2001;3:422–6). Our similar study design with the use of the EAUS was used in the past in the management of patients treated by a synthetic plug and published a few years ago (Colorectal Dis. 2012;14:e264-9), with good results.
We totally agree with you about the efficacy of the MRI in the evaluation of anal fistulas; however, the Literature has clearly shown that both the techniques are equally effective in the management of this kind of patients, and EAUS had comparable (and sometimes better) results than MRI (Colorectal Dis. 2001;3:189-97; Dis Colon Rectum. 2012;55:576-85; Gastroenterol Res Pract. 2016; doi: 10.1155/2016/1895694. Epub 2015 Dec 27). At present, a new multicentre study is further evaluating this device, and this time we included also a preoperative and postoperative MRI evaluation: it will be very interesting to compare the two imaging techniques in the postoperative evaluation of the patients implanted with this device.

4) Ethics committee approval date and number should be indicated at the beginning of the methods section.

Answer: thanks, we have modified the text in the "Methods" section.

5) Median age of the patients is 65. This is surprising... It is an unusual age for anal fistula. How many patients were treated for anal fistula during the study period? How many of them were eligible for

the study?

Answer: we know that the median age of this series is high and unusual, however is the reality, so we cannot change it. The median age was simply influenced by the presence of four patients aged more than 80 years: given the small sample size, their age heavily influenced the pooled value. Age and other demographics of all patients are detailed in Table 1.
During the 4-months study period we evaluated about 30 patients affected by anal fistula and the exclusion of that patients was due to several reasons (i.e. example persistent sepsis, too low tract...)

6) Again, irrigation of the tract by antibiotics is not a common practice. Is this their routine?

Answer: irrigation of the tracts by antibiotics is not our routine in the treatment of anal fistulas and, as already indicated in the question n°2, we decided to have some extra-precautions in this preliminary study. However, an implant of the device without antibiotics irrigation could be evaluated.

7) Authors tell that patients underwent seton placement prior to the procedure whenever necessary; however, they do not declare how many of the study patients needed seton placement. This should be identified.

Answer: the pre-operative use of setons is clearly indicated in Table 1. However, nine out of ten patients underwent a setons placement prior to device implant.

8) 6-month follow up time is short. What was the median FU time?

Answer: we totally agree with you remarking the need of a longer follow-up; indeed the final sentence of our conclusions goes in this direction. All patients attended the 6-months FU visit. When we submit the paper (March 2016), the median FU was 12 months and the healing rate is the same (only a telephone interview).

9) Authors declare that a patient with failed procedure later underwent fistulotomy. As very well known, fistulotomy is the gold standard treatment whenever possible. Why one should use a more expensive and less effective method when fistulotomy was possible and did not seem to harm the continence?

Answer: as known a traditional fistulotomy is the gold-standard whenever possible, but is well known also that there is a risk of postoperative continence impairment. So, at our institution we think that a minimally-invasive technique, if possible, should be offered as a first-line treatment in case of a complex fistula. In this specific patient the device implant failed, the patient underwent a new setons

placement to reduce the flogosis, and then, also thanks to a spontaneous reduction of the fistula length, a traditional fistulotomy was carried out with success. However the postoperative risk of fecal incontinence was taken into account when signing the patient's informed consent.

10) A recent study about autologous cartilage plug placement for the treatment of anal fistula declares similar success rates in a longer FU time. Authors might want to have a look at that study and comment on the comparison of their study to the cartilage plug. (Ozturk E. Treatment of recurrent anal fistula using an autologous cartilage plug: a pilot study. Tech Coloproctol. 2015;19:301-7)

Answer: thanks for the suggestion. We have modified the text in the "Discussion" section.

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COMMENTS TO AUTHORS

It is a very interesting manuscript presenting promising results of an improved plug for complex fistula treatment. My main concern of this manuscript is related to the conflict of interest statement. To my knowledge, the authors of any podium presentation at the the ASCRS Annual Meeting have the commitment to publish the work in the Journal Diseases of the colon and rectum. Please clarify this matter.

Answer: we know of this commitment; indeed, we asked them to have some clarifications about the submission process to the journal: they said us that the paper was accepted in a special symposium entitled "New technology", and that the presenters in this symposium were not intended to be subjected to mandatory submission to Disease of the Colon and Rectum. For this reason we decided to submit the paper to World Journal of Gastroenterology.

In the surgical procedure a couple of clarifications are would be helpful- Has been achieved an

hermetic closure of the internal orifice?

Answer: the internal opening was closed with a resorbable "z-stitch" and the disk was anchored to the internal opening with the same suture in order to cover the closed internal opening.

The term "unsheathed" should be explained for a better understanding of the procedure.

Answer: thanks for the suggestion, we have modified the text in the "Methods" section.

The description of the fistulas do not include the presence of cavities, ?could be added this information?

Answer: the removal of the cavities along the fistula tract is of crucial importance to reduce the risk of recurrence or persistence of the disease; we think that our protocol reduced this possibility by two technical steps: 1) the placement of a draining seton is aimed also to consolidate the fistula tract reducing all the cavities; 2) the fistula tract was prepared for the device placement by cleaning and debridement of the tract, to remove and clean all cavities (curetting and brushing with a small endoscopic brush). We slightly modified the "Methods" section to clarify this concept.

LIFT and other plugs are discussed in the manuscript, but Cell therapy, being a minimally-invasive technique for the treatment of complex perianal fistula is not mentioned. Introducing this technique may enrich the discussion.

Answer: thanks for the suggestion. We have modified the "Discussion" section.

The extrusion of the device happened in the patient with the wide track, and the device seems to be thin. This device could be probably useful in long and thin fistula track. If appropriate, this reflexion could be added to the conclusion.

Answer: thanks for the suggestion. This concept could be acceptable, and "it sounds well". The "Discussion" section already contains a sentence about your suggestion concerning the efficacy in longer tracts. However, at present, due to the small sample size of this study, we have not sufficient data to support this possibility. Now, we are conducting a new larger multicentre study to obtain more information, and we think that your suggestion will be surely evaluated during the future analysis of the results, with a specific subgroup analysis.

Minor typing errors should be reviewed for example in the 3rd line of the introduction "managementbecouse" is written together.

Answer: thanks. We have modified the entire text by checking and removing these unintentional errors determined by the software that we used.

Acronyms FU and CCFI should be written with brackets the first time the term appears in the text (FU and CCFI)

Answer: thanks. We modified the text.