

Oct 15, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: ESPS Manuscript No 13736-review.doc).

Title: A modified topical formalin irrigation treating hemorrhagic chronic radiation proctitis

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 13736

The manuscript has been improved according to the suggestions of reviewers:

1. Format has been updated

2. Revision has been made according to the suggestions of the reviewer

(1) reviewer No. 70818: This study has several significant problems: - This is a retrospective small series of patients. - There is no novelty in the treatment and no comparison to any other treatment modality. - There is no mention in the manuscript to the standard of care for radiation proctitis, which is endoscopic argon plasma coagulation control of bleeding lesions. - The language is poor.

Respond to the reviewer:

① retrospective: the nature of a retrospective study with thirty-one patients enrolled was inevitable, which may bring in potential bias. But we shared our experience of a modified formalin irrigation and assessed the efficacy and safety in treating hemorrhagic chronic radiation proctitis (CRP). And the result can provide evidences for further prospective randomized-controlled trials to confirm it.

② novelty: there were published studies which covers different ways and concentrations to apply formalin in the lesions of CRP patients, but high rate of complications were reported. Here, we modified topical formalin irrigation to focus on the safety and low rate of complications were observed in our series. The details about safety are listed below (which was also mentioned in the discussion section): protection of internal sphincter (spinal epidural anesthesia and the clasp knife position provided a full anal dilatation instead of dilatation violently by an anal retractor); protection of proximal normal colon mucosa (A Foley catheter was inserted into the proximal sigmoid cavity in order to prevent the backflow damage of formalin, which can reduce risks of colitis and peritonitis); more targeted at lesion area (a semicircle anal speculum was used for visual formalin irrigation, which can prevent the normal rectal mucosa, superficial ulceration, the anal canal and skin of perianal from formalin damage); well controlled volume and irrigation time of formalin towards lesions (a small volume (10-20ml) of 4% formalin and a short time (less than 5 minutes), which was reported as a safe way).

③no mention to standard treatment options: content that compared to endoscopic argon plasma coagulation (APC) for hemorrhagic CRP was added to the discussion section- "Many medical treatment options have been tried to help control rectal bleeding in CRP patients. Sucralfate, 5-aminosalicylic acid, metronidazole, steroids and fatty acid have been reported and the results are inconsistent and unsatisfactory. Endoscopic treatment modalities such as argon plasma coagulator is considered to be an effective and popular option for patients with refractory hemorrhagic CRP; however, APC therapy can bring in morbid outcomes, such as rectal ulceration, stricture, bowel perforation and even rectovaginal fistulas. In our clinical centers, we used APC for several patients with hemorrhagic CRP. The results were satisfactory for patients with limited surface areas of lesions, but for patients with massive areas of telangiectasis, complications such as anal pain, tenesmus and rectal stricture were observed. Topical application of formalin is considered to be a safe and effective way to treat hemorrhagic CRP with comparable efficacy and less complications as APC".

④the language was polished for the whole manuscript.

(2) reviewer No. 180872: few minor comments-The method of application is repeated 3 times in the text (abstract, methods and in the discussion) Installation or irrigation may be more appropriate than application for the technique. Other treatment options like endoscopic plasma coagulation should be discussed.

Respond to the reviewer:

① we adopted the reviewer's advice to described the method detailedly in the method section, and deleted the repeated detail description in the abstract and discussion section.

② "formalin irrigation" was used to replace "formalin application" in the revised manuscript according to the reviewer's suggestion, for the former seems to be more appropriate for the modality we used.

③ Other treatment options like endoscopic plasma coagulation are discussed in the discussion section as above.

(3) reviewer No. 2569785: MAJOR ISSUES - TITLE "Modified formalin application": modified compared to what? The authors should highlight and describe in detail which is the novelty of their technique. This could help to increase the interest of the paper. Otherwise this is just one more series describing the use of formalin in CRP. - METHODS: how many patients were excluded from the study? Please detail for each exclusion criteria. - Who performed the follow up? - How was evaluated the defecation function? - How was evaluated the normal distribution of the continuous variables? - RESULTS: the first two sections must be resumed. They are just a copy of the Table 1. - Continuous variables should be expressed as mean and standard deviation when normal and as median and range when not normal. - Follow-up should be expressed as median, not mean. - "After a mean 28... treatment": data on recurrence must be expressed using actuarial rate and represented by a Kaplan-Meier curve. - Univariate analysis of variables associated to efficacy should be better performed with log-rank test or cox regression. MINOR ISSUES - Authors use HRP in the abstract and CRP in the paper: please uniform the abbreviations and use it throughout the whole text. - METHODS: Table 2 is the first cited in the text: it should be renamed as "table 1" - Revise SPSS producer (I think now it is produced by IBM) - RESULTS: "No recurrence... malignancies": at what time? During ALL the follow-up? - please rephrase as "rectal resection with pull-through coloanal anastomosis..") - "Potential risk factors": for what?

Respond to the reviewer:

① modified compared to what? : we conducted the procedure of formalin irrigation in the operation room under spinal epidural anesthesia and the clasp knife position, which was different from previous reported studies of formalin used under endoscope or used in topical anesthesia in the wards without protection of proximal colon mucosa. The modified formalin irrigation provided a full anal dilatation

instead of violent dilatation by an anal retractor, thus may prevent the internal sphincter from damage.

② novelty was described in the discussion section as mentioned above in “response to reviewer No. 70818”.

③exclusion criteria of formalin irrigation in our series: patients with larger ulcers, necrosis of mucosa or stricture (Vienna Rectoscopy Score-VRS: 4-5 points); patients with severe life-threat bleeding or mild bleeding which can be controlled by medical treatments; patients allergic to formalin; and patients with relapse of primary tumor. And the exclusion criteria were added to the method section of the revised manuscript.

④ follow-up: Yuan ZX and Liu YQ performed the follow-ups by telephone. The defecation function was evaluated through patients’ descriptions about such as stool frequencies, bleeding severity, existence of tenesmus, fecal incontinence (or sanitary pads used per day), constipation and anal pain. And these information were added to the method section.

⑤ The normal distribution of continuous variables: continuous variables described in Table 2 including age, total irradiation dosage, time from the end of radiotherapy to bleeding, duration of bleeding and preoperative hemoglobin level were evaluated by Shapiro- Wilk test for normal distribution. If the variable is normal distributed, *t*-test and mean and standard deviation of the variable were adopted; if not normal distributed, Wilcoxon rank sum test and median and range were used, according to the suggestions of the reviewer. And we revised the related section in the manuscript.

⑥the first two sections has been resumed and follow-up was expressed as median; response rate was expressed using actuarial rate; some patients didn’t respond to formalin from the first usage of formalin, which can’t be defined as recurrence, so recurrent rate was not easy to calculate and a Kaplan-Meier curve was not conducted (a small sample size of the study is also not appropriate for the curve); we deleted univariate analysis of risk factors associated with efficacy of formalin because some patients responded to formalin in the short-term, but failed later, while some other patients didn’t respond to formalin in the short-term, but bleeding got remission in the long-term. Thus it is difficult to differentiate response and unresponse to formalin.

⑦we have uniformed the abbreviations such as CRP and use it throughout the whole text. “Table 2” has been renamed as “Table 1”. SPSS producer has been replaced by IBM in the revised manuscript.

⑧“No recurrence...malignancies” was replaced by “No recurrence or metastasis was found for primary pelvic malignancies during follow-up”, but for seven patients who were lost to be followed.

we were not sure about their survival status.

⑨"Potential risk factors" has been deleted.

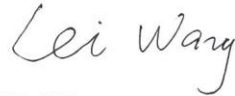
⑩"rectal resection with pull-through coloanal anastomosis.." was rephrased in the results as "Park's operation (a sphincter-saving operation which involved the resection of rectum and the perianal anastomosis of healthy colon to the anal canal, the details were described previously...) and one reference about the operation was added"

(4) reviewer No. 2411071: English needs a little polishing.

Respond to reviewer: language has been polished for the whole manuscript.

Thank you again for publishing our manuscript in the World Journal of Gastroenterology.

Sincerely yours,

A handwritten signature in black ink that reads "Lei Wang". The script is cursive and fluid, with the first name "Lei" and last name "Wang" clearly distinguishable.

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