4.10.2016

Dear Editor

World Journal of Gastrointestinal Surgery

Re: Perforated Peptic Ulcer- An Update, ESPS manuscript NO: 28885

Many thanks for getting 5 peer reviewers for our above reference manuscript. We are delighted that none of the reviewers have recommended a 'rejection'. We find the comments and critic of all the reviewers very constructive and we believe that the amended version of manuscript would be a high quality manuscript upholding the standards of our journal.

We herewith provide a point to point response to reviewer comments and we have made changes in the manuscript accordingly. The changes in manuscript are marked with an underline. The deleted part of the manuscript is mentioned in this letter.

We shall start with Editorial comments stated along side the manuscript.

Editorial comments:

1. Family names – Chung and Shelat. Both these are family names and we have underlined them.
2. We have added the postcode at both places as requested.
3. We have attached the signed .pdf file for Conflict of Interest.
4. I have amended the citation part for second author – earlier it read as Vishal GH. This was incorrect. We have amended this to Shelat VG as 'Shelat' is the family name.
5. We have put the reference number is superscript and square brackets as requested.
6. We have added the audio core tip as requested.

We would now like to address reviewer comments. We have marked the changes in manuscript with underlines. We have responded point by point to the comments.

First reviewer

Reviewer's code: 00013033

Reviewer's country: Hungary

Comments: This is a comprehensive, well-written paper on the perforated peptic ulcer disease.

1. Abstract and core tips should be rewritten and references should be removed.
   Response – We have deleted the references from abstract and core tip. We have added the following statement in Abstract section to make it complete - Gastrectomy is recommended in patients with large or malignant ulcer.
2. Authors should also decide if they would like to cover the full spectrum of the disease or only the perforated cases, the separation and aims are sometimes not clear.
   Response – Yes, agree. Sometimes it appears that PUD is stated and that may dilute the PPU part. We have deleted the following 2 statements from 'core tip'. Peptic ulcer disease (PUD) affects 4 million people worldwide annually. PUD can now be treated with medications instead of elective surgery.
   We agree that core tip should contain only PPU related information and our focus is PPU and not PUD. Some base PUD data is presented in opening statements to provide overview of disease burden.

Second reviewer

Reviewer's code: 00503404

Reviewer's country: Hungary

Comments: A mainly well written review paper, authors should include one or two Tables high lighting the major non-surgical and surgical studies with outcomes in the treatment of PUD.

Response: We are thankful to reviewer for applauding our efforts. We agree that addition of tables would be interesting. We believe that adding information on PUD would dilute our intention of focus on PPU. Actually, one of the reviewers has already suggested reducing the focus on PUD. Hence we shall take liberty not to add stuff on PUD. The focus of our manuscript is a 'review' and not a summative analysis which is required for systematic review and hence we have not tabulated the information.

Third reviewer

Reviewer's code: 03646666

Reviewer's country: 0

Comments: A comprehensive and a well articulated review paper on PUD regarding the recent advancement in medication and avoidance of laparoscopic surgery.

Comment 1: Figure 3. needs to be looked at, although the figure is very informative I would suggest authors to revise this figure to make is more easy to read and understand.

Response: Thank you for applauding our efforts on this review manuscript. We agree that Figure 3 can be difficult to understand. We agree that this figure is very information and we are thankful to you for acknowledging this. In fact, the senior author (VGS) has used the same figure in close to 5 of his manuscripts (PMID:27619359, PMID: 27074924, PMID: 26133908, PMID: 26033361 and PMID: 2138071) and this figure is well received. Also, our Editor has requested us to provide him with 'ungrouping' of the Figure and we are sure that they shall make it more 'nicer' to enhance its impact. We have not made any changes for now.

Fourth reviewer

Reviewer's code: 00503686

Reviewer's country: Egypt

Comments: It is a very good and comprehensive "chapter" of a book, but I am sorry to say it is not suitable (in my opinion) for publication in the journal.

Response – Many thanks that you have really equated our review paper worthy for 'book chapter'. We would certainly take this complement. A typical book chapter is 'too outdated' by the time the book is published and hopefully we have taken care in our review that we provide most updated information to our reviewers. In this spirit of keeping the review most current, we have actually added recent publications on PPU. These publications are published after we submitted our manuscript for peer review. We have done a literature review and come out with some new additional important and relevant papers which we have cited. We have added the following statement - In recent time, majority of the published studies describe marginal ulcer and its perforation following bariatric procedures. We have reported a series of nine patients with marginal ulcer perforation following previous gastric resections for benign and malignant diseases[112]. We have concluded that patients with marginal ulcer do not present with septic shock. Also, revision of Billroth II gastro-jejunostomy to Roux-en-Y anastomosis is not mandatory and omental patch repair is sufficient [112].

There is a recent publication from our sister institute and they included data of our patients. The authors concluded that Laparoscopic repair is superior to open repair in patients with MPI > 21 and in selected cases with presentation within 48 hours and ulcer size < 2 cm. This was a retrospective case matched study. We have added – 'In a recent study including 148 patients from two university affiliated hospitals in Singapore, Lee JK et al has reported that in selected patients with presentation within 48

hours and ulcer size < 2cm, laparoscopic repair reduces length of hospital stay compared to open surgery in patients with MPI > 21[125].

Ref 112 and 125 are added and all other references are adjusted.

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Fifth reviewer

Reviewer's code: 00004764

Reviewer's country: United States

Comments: Your narrative review examines the topic of perforated peptic ulcer. It is relatively comprehensive and focuses somewhat on medical issues which today are very important. I have made suggestions for additions and modifications which I hope will improve its overall quality. Specific comments:

1. You comment under H. pylori that recurrent PUD mainly occurs in patients with H. pylori infection. This is also very common in those who continue to use NSAIDs. Also, the risk of recurrent H. pylori infection is significantly reduced with proton pump inhibitor therapy. In contrast, proton pump inhibitors have only a modest efficacy for reduction in ulcers with NSAID users. The section on genetic predisposition likely is of low interest to the reading audience.

   Response: Oh yes. We have added this statement. It is underlined in main file under H. pylori section. We added - The risk of recurrent *H. pylori* infection is significantly reduced with proton pump inhibitor therapy, but proton pump inhibitors have only a modest efficacy for reduction in ulcers with NSAID users.
   We have decided to keep that genetic statement. However, we completely agree its low interest and hence have deleted the statement – 'In contrast, *DQA1*0301* allele was lower in these patients'. We have also omitted the special sub heading of genetic predisposition and now have merged this with 'others'. This will reduce the emphasis on genetic aspect.

2. I would make several more comments about Zollinger-Ellison syndrome. This is a cause of perforated peptic ulcer that must be excluded in every patient.

   Response: Thanks. We have added some stuff o ZES. We also have created a short form ZES for this as we had to repeat this term a few times. We have added - Over 90 percent of patients with ZES develop peptic ulcers and

typically these ulcers are refractory to proton pump inhibitor therapy. ZES should be suspected in patients with multiple or refractory peptic ulcers, jejunal ulcers, family history of PUD and associated diarrhea. All patients with ZES should be screened for Multiple Endocrine Neoplasia 1 (MEN1) syndrome.

3. You comment about alcohol consumption which is controversial and likely does not cause ulcer. It does cause increased acid production but, again, is not associated with ulcer.

   Response: Yes. Absolutely true. We did uptodate literature review and confirm your comment. This is very important point. We have to include this into our review. We have added - Despite these acute effects, there is no evidence that alcohol causes PUD.

4. Under Diagnosis – it's also possible that free air under the diaphragm represents another diagnosis such as perforated diverticulosis. Clearly at most centers a CT scan is going to be performed which can generally differentiate these causes and exclude other etiologies.

   Response: Yes. True. We have modified the statement – 'When erect chest x-ray establishes a diagnosis of PPU, no further imaging is required'. Now the above statement is deleted. It is replaced with - In a patient with upper abdominal symptoms, free air on an erect chest x-ray establishes a diagnosis of PPU.
   Our concluding statements in diagnosis section do mention the utility of CT scan even in patients with free air on CXR. So that aspect is covered.

5. Using oral contrast would likely be important when peptic ulcer is considered to exclude active leak and thus the likelihood that surgery will be required.

Response: Yes true. We have stated the role of oral dye study and we assume that this statement is in relation to CT scan oral contrast!? Regarding CT scan, even if contrast is not leaking but if there is free air near the hepatoduodenal ligament, it is

suggestive of PPU. We have added a statement - Oral contrast with CT scan is a useful tool and if free leak is seen, diagnosis is certain.

6. Under Figure 1 – the chest x-ray is of poor quality.

Response: Ok. This is real life in emergency unit. Not all CXR are standard high quality! We shall keep this CXR as it belongs to the same patient as CT scan image. No changes are made.

7. Under Management – what is "surgical source control"?

   Response: This phrase means control the source of contamination by surgery. We have used this general broad phase to avoid types of surgery (omental patch, gastrectomy etc) and also emphasize that surgery controls the source of sepsis i.e. perforation. Four additional reviewers have not raised issue with this term and again on reading our manuscript, we believe this is simple and self explanatory term and hence we decide to leave it as it is.
8. When discussing drug treatment in ulcer you describe "triple therapy". I would use the term triple therapy for H. pylori infection.

   Response: OK. We have changed the statement to - Omeprazole and triple therapy for H. pylori eradication are useful adjuncts in treatment of PPU.

9. In a patient presenting with perforated peptic ulcer, it seems that one would want to exclude H. pylori infection rather than empiric treatment. In addition, if H. pylori infection is identified, then follow-up to ensure eradication is paramount. At the time of presentation one could consider a stool antigen. Blood tests for antibody are less sensitive and specific unless in areas of high prevalence. Clearly excluding causes by history or laboratory studies is important. Long-term PPI therapy would be important until the exact cause may be identified and treated (example H. pylori infection). Also, it is important to exclude occult NSAID user as recurrent ulcer disease is very common in such patients.

Response: In a patient with PPU, goal is to manage PPU. Senior author (VGS) is not aware of any unit doing stool antigen in emergency setting of PPU. Any investigation after proton pump inhibitor therapy may be inaccurate and hence empiric therapy is justified. Also we agree that at next opportunity, testing should be done for H Pylori. We are not a proponents of 'long term proton PPI'. Two reasons – (a) what is long term defined as ? (b) Sufficient evidence that this is harmful e.g. vit b12 deficiency, electrolyte deficiency, vit d deficiency, clostridium difficile infection etc. We treat with 'triple therapy'. At follow-up we do Urea Breath Test and establish H Pylori is eradicated. NSAID is a part of history + national electronic records whereby drug history can be checked for all patients. We have added - We perform urea breath test to establish H. pylori eradication after completion of medical treatment.

10. You comment that there may be a high mortality rate if conservative management fails. I assume in this situation that CT scan with oral contrast to exclude active leak would be important to reducing such mortality.

    Response: Of course. One of the criteria of non operative management is – no active leak. So active leaking patients are not candidates for non operative management (unless they are prohibitive risk of surgery i.e. ASA 5). We have mentioned the principles and perils of non operative management.
11. Vagotomy is also less likely to be performed as one can identify and eradicate H. pylori infection.

    Response: Yes. True. We have stated –'Nonetheless, vagotomy is now seldom performed for PPU due to the availability of medications such as histamine receptor antagonists and proton pump inhibitors.' We added H. pylori aspect to that!.

12. You do not tell us specifically when gastric resection should be performed. You do mention some risk factors but your comments would be welcomed.

    Response: We have mentioned the following statement – 'Nowadays, emergency gastrectomy is reserved for a giant ulcer or a suspicion of malignancy when it is not safe to perform omental patch repair[77]. '

Our algorithm of management of PPU is published earlier. Ref 51 - Int J Surg. 2015;14:38-44. At present time, there are no clear cut indications for gastric resections. What we know is stated in manuscript.

Our view – Gastric resection is done in sick patients where surgeon feels leak may occur due to patch failure. In cases of suspected malignancy – no questions asked – gastrectomy is clearly indicated. In first scenario – surgeon judgement of leak – he performs gastric resections so he can avoid a leak. In our experience of managing 770 patients with PPU, gastric resections actually paradoxically have high morbidity. So currently we are in the process of doing a propensity score matching study to compare patients with resection versus patch repair after matching for risk factors. Results are awaited. There is no randomized study to answer this question.

13. You mention Boey's score and perhaps you should tell us what this represents. You mention this later in the manuscript.

Response: Thanks. We have mentioned all the scoring systems. We initially wanted to make a table of all systems and then realised that previously this is already done by others and doing so would be duplication and may even amount to plagiarism. We want to be safe. We have stated Ref 51 where all the details can be accessed by readers who are interested.

14. Dissemination is misspelled after bacteria.

Response: Thanks. We have corrected the error.

15. What is the tire test?

Response: Thanks. We have never done this test. This is described in literature and hence we have mentioned this for sake of completeness. We have changed the statement to –' Nowadays, the tire test (watch for bubbles after submerging patch repair under water) and the dye test (to inject dye via nasogastric tube) to look for leakage after closure of PPU are rarely used.'

16. When you discuss endoscopic stenting, I assume you meant fully covered stents. One might suspect that this would work better for a post-op leak rather than an initial perforation.

    Response: Yes. All is true. Our subheading on stents mentions Ref 103 and 104 which are the two studies on stents in patients with PPU. Our focus being PPU, we have not elaborated the role of stents in all kinds of post-operative leaks.

17. You state that perforation is a "serious complication". That seems to lessen the importance of death!

    Response: Not at all. Death is ultimate. Perforation is 'serious' indeed! Unrecognized, untreated will lead to death. Let's keep that please.

18. You also mention that it carries a higher mortality risk although the data suggests the mortality rate is relatively low. Perhaps you mean the morbidity is great.

    Response: Our database of 770 patients over 10 years shows mortality is close to 8%. There are reports of <5% mortality and also reports of up to 20% mortality. We believe that mortality has reduced, but would still keep as 'high'. So we indeed mean 'mortality' and not only 'morbidity'.

We are indeed very appreciative of time taken by all the 5 reviewers, especially Reviewer 5 to make detailed comments that will really enhance the quality of our manuscript.

Thanking you

Vishal G Shelat

Chung Kin Tong