

Format for ANSWERING REVIEWERS



March 01, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 8982-Review.doc).

Title: Complications after ileal-pouch anal anastomosis in Korean patients with ulcerative colitis

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Necessary changes have been made to the manuscript based on reviewer's suggestions.

1. Format of the manuscript has been updated.
2. Revisions have been made according to the reviewers' suggestions

(1) We want to thank the reviewer for their detailed and comprehensive review of our manuscript. We appreciate your kind suggestions on how to improve the overall quality of this study. In particular, we strongly agree that the pouch bleeding might be one of the early signs of acute pouchitis. We also agree that acute pouchitis can present itself with significant bleeding resulting in a severe anemia. However, our patients exhibited symptoms of acute pouch bleeding within 48 h of operation. These acute bleedings were resolved after transfusions. Thus, we concluded that these bleedings most likely originated from the ileal mucosa of the anastomosed staple lines. However, since we did not confirm the cause of bleeding with endoscope, some acute bleedings might have been a result of acute pouchitis. Therefore, a new sentence, along with recommended references, was added stating that acute pouchitis might have caused the pouch bleeding in early postoperative periods. Based on your recommendation, we had a GI pathologist reevaluate histopathology results of the five rectovaginal fistula cases to confirm

UC. Diffuse chronic inflammation, with no ileal inflammation, and diffuse crypt changes with atrophy, distortion, or villiform surface were found in these pathologies. All of these features favor UC over Crohn's disease (reference no 30). A sentence was added stating pouch vaginal fistulas can develop more frequently in Crohn's colitis, and they are usually more complex than those of UC. However, numerous studies have reported that pouch vaginal fistulas can also develop in UC patients with either pelvic sepsis or when technical problems are encountered (references 4 and 15). Majority of our patients presented with a relatively simple type of fistula and were treated with transanal advancement flaps or ileostomies. Only one patient had a pouch failure from recurrent fistulas. We considered that the fistulas could have developed as a result of a severe pouchitis after UC treatment with IPAA.

Based on reviewer's recommendations regarding stoma distinction, we performed diverting loop ileostomies in 71 IPAA patients. We did not undertake any terminal ileostomies due to lack of emergent subtotal colectomies. Only one patient, with a pouch failure and subsequent pouch excision, underwent a permanent end ileostomy. Upon your advice, information on a diverting loop ileostomy, constructed in 71 (98.6%) patients and closed after a median period of 4.4 months, was added to the manuscript.

(2) Thank you for your kind comments and detailed review of our manuscript. The abstract was rewritten for easier readability. The statistical digits were changed based on your recommendations ($P = 0.002$; HR, 14.8; 95% CI, 2.59 - 84.5; $P = 0.016$; HR, 6.69; 95% CI; 1.43 - 31.3). Significant digits were also corrected for in the manuscript and Tables.

(3) Thank you for your kind review and comments of our study. One of the explanations for the lower rate of pouch failure compared to the Western reports may be due to the differences in ethnicity or dietary habits. Lower incidents of indeterminate colitis in our study may also be one of the reasons for better outcomes. Earlier Japanese studies also reported the lower rate of pouch failure, suggesting that Asian countries might achieve better outcomes in IPAA treatment of UC. However, further studies are necessary to confirm this statement.

We would like to clarify our statement regarding anti-inflammatory drugs and their role in postoperative complications. Although we do not believe that anti-inflammatory drugs are a predictor of postoperative complication, we do think that these complications may be more difficult to manage due to these drugs, such as steroids. To eliminate any confusion that may arise from our previous statement, we removed the anti-inflammatory drugs part away from the sentence in the manuscript. Furthermore, we listed all of the anti-inflammatory drugs, such as 5-aminosalicylic acid, azathioprine

and steroids, taken by all of our patients. The median follow-up period was 82.5 months and pouch failure rate was 2.8%. A study of meta-analysis published by a Dutch team, pooled with more than 40 western studies, reported a pouch failure rate of 6.8% in a 36.7 month follow-up period. The pouch failure rate increased to 8.5% in follow-up period of more than 5 years in the study (reference no, [8]). Therefore, our follow-up period was sufficiently comparable to western studies. We do, however, agree with you that pouch failure rate will most likely increase with longer follow-up periods, which has been stated in the manuscript.

Our pouchitis rate was 23.6% compared to Western study which reported pouchitis rate of 18.8%. Pouchitis was identified as one of the most important risk factors for complications in our study. Many studies have shown an association between pouchitis and subsequent pouch-related complications. It is clear that pouchitis should be managed appropriately to achieve better outcomes. To reiterate this point, in the discussion we added a statement on the importance of early detection, aggressive medical and surgical treatment in achieving better outcomes. The manuscript was edited by an English language editing company (AmEditor: www.ameditor.com) recommended by your journal.

3. References and typesetting were corrected

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

Sincerely yours,

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