

April 15, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 2579-review.doc).



Title: Utility of Single and Double Balloon Endoscopy in Patients with Difficult Colonoscopy - a Randomized Controlled Trial -

Author: Atsuo Yamada, Hirotugu Watabe, Noriyuki Takano, Goichi Togo, Yutaka Yamaji, Haruhiko Yoshida, Takao Kawabe, Masao Omata, and Kazuhiko Koike

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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

Reviewer 1

The authors compared SBE with DBE in patients with previous incomplete colonoscopy because of several reasons. They achieved excellent total colonoscopy rates (91% v.s. 100%) even in these difficult cases. These results indicate the utility of SBE and DBE in patients with incomplete conventional colonoscopy. The tables and endoscopy pictures are informative, the discussion is short and clear. Only some minor questions may arise:

1.) Why did not administrate the authors sedatives during the endoscopy however, all cases were technically difficult base on the previous colonoscopy failures?

→We appreciate the reviewer's suggestion. In order to assess the difference between single-(SBC) and double-balloon colonoscopy (DBC), not the utilities of sedative drugs, we did not use sedatives during the procedure. In terms of colonoscopy, several papers reported that conventional colonoscopy without sedation is feasible, effective and well tolerated^[1, 2] On the other side, most of previous papers regarding SBC and DBC used sedative drugs ^[3-7]. Although the pain score during for procedure was slightly high, all of the present study patients did not request to stop the procedure. The present paper indicated that both SBC and DBC can be performed without sedation. We added the following sentences in page 7 in discussion;

The present study showed that SBC and DBC can be performed safely without sedation even in patients with incomplete total colonoscopy using a conventional colonoscope. In terms of colonoscopy, several papers reported that conventional colonoscopy without sedation is feasible, effective and well tolerated^[1, 2] On the other side, most of previous papers regarding SBC and DBC used sedative drugs ^[3-7]. Although the pain score during for procedure was slightly high, all of the present study patients did not request to stop the procedure. The present paper indicated that both SBC and DBC can be performed without sedation.

2.) Did the authors use CO2 or air insufflations?

→We appreciate the reviewer's suggestion. We did not use CO2 gas in the study. We used air insufflations for the both procedures. CO2 gas pump for both balloon endteroscopy was not yet available at the beginning of this study in Japan. CO2 gas is expected to ease endoscopy. We added the following sentences in page 4 in methods;

Air insufflation was used during the both procedures.

3.) In one of the SBE cases the cecal intubation time was as long as 85 min, which was close to the 90 min limit being insertion time limit with conventional colonoscopies. How the authors comment this?

→We appreciate the reviewer's suggestion. Difficult cecal intubation is associated with female gender, old age, a low body mass index (BMI), diverticular disease, and previous abdominal surgery ^[8-11] . This patient had three risk factors of difficult colonoscopy (old age, low body mass index and previous abdominal surgery). Consequently, even single-balloon endoscopy (SBE) made redundant loops and it took longer time to insert into the cecum.

4.) The colorectal polyp detection rates were higher (45% and 30%) than with the usual one by colonoscopies. Were these polyps all adenomas? Do these authors conclude that by enteroscopes one can find even small polyps more precisely than with colonoscopies?

→We appreciate the reviewer's important suggestion. All polyps were histologically confirmed as adenoma. We reported that the prevalence of colorectal polyps by conventional colonoscopy in our cohort was 44.3% (303/684)^[12]. There were no differences between both balloon colonoscopies and conventional one ($p = 0.66$). Prevalence of colorectal polyps is influenced by patient background such as age, gender, race, percentage of positive fecal occult blood, past history of colorectal polyps, and so on. We added the following sentences in page 5 in results;

All polyps were histologically confirmed as adenoma.

Reviewer 2

Dear Author, I have read with great interest your paper addressing an interesting comparison between single and double ballon enteroscopy for difficult colonoscopies. The paper is well written, the design and methods appropriate and the discussion well focused on the results and previous reports. The only drawbacks I see in the paper are the short number of patients included, and the lack of sedation for this patients, for colonoscopy and for enteroscopy. From a western perspective, nowadays performing colonoscopy or, even more retrograde enteroscopy, is unthinkable without sedation, which in most centers in Europe is administered by the endoscopist. This way, our rate of cecal intubation is higher and the needs of enteroscopy lower. I also doubt whether with only 21 patients the conclusions achieved by the authors are accurate, and represent the truth in clinical practice. The authors did not even perform a multivariate analysis in this population (it is impossible with this number of patients). That is why I have some reservations about the results, or its applicability of clinical practice. Kind regards.

→We appreciate the reviewer's suggestion. We agree with the reviewer's comment. Difficulty of colonoscopy may be different between Western and Japanese settings. Difficulty of colonoscopy is influenced by many factors including sedations, BMI, age, gender, history of abdominal surgery, etc ^[8-11]. Precisely, the present paper showed that both SBC and DBC can archive total colonic examination in Japanese patients with difficult colonoscopy without sedative drugs. The authors also think that sedative drugs make it easy to conduct SBC as well as DBC, likewise conventional colonoscopy. In terms of colonoscopy, several papers reported that conventional colonoscopy without sedation is feasible, effective and well tolerated ^[1, 2]. On the other side, most of previous papers regarding SBC and DBC used sedative drugs ^[3-7]. Although the pain score during for procedure was slightly high, all of the present study patients

did not request to stop the procedure.

The prospective study showed that the utility of SBC and DBC for difficult colonoscopies seems comparable in relatively small number of patients. The authors also think that a larger prospective non-inferiority trial is needed to elucidate any difference in the utility of SBE and DBE. As a matter of fact, we calculated a required sample size which is able to evaluate the feasibility of non-inferiority comparison between SBC and DBC for the primary end point of cecal intubation rates. Based on the results of the previous reports, we assumed the success rate for SBC was 0.90 and that for DBC was 0.95. The sample size was 343 patients (172 in each arm) when calculated based on a margin of non-inferiority for a success rate of 0.10 with a statistical power of 80% and a one-sided type I error rate of 0.05. Ideally, multivariate analysis elucidates some important findings, as the reviewer suggested. The number of the study is too small to conduct multivariate analysis. Instead, the present study acquired high evidence level by conducting a randomized controlled trial.

We added the following sentences in page 7 in discussion;

The present study showed that SBC and DBC can be performed safely without sedation even in patients with incomplete total colonoscopy using a conventional colonoscope. In terms of colonoscopy, several papers reported that conventional colonoscopy without sedation is feasible, effective and well tolerated^[1,2]. On the other side, most of previous papers regarding SBC and DBC used sedative drugs^[3-7]. Although the pain score during for procedure was slightly high, all of the present study patients did not request to stop the procedure.

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3 References and typesetting were corrected

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

Sincerely yours,

A handwritten signature in black ink, appearing to read 'Atsuo Yamada', with a stylized, cursive script.

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