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Reviewer # 2554592

1. This article about “Evidence to suggest adoption of water exchange deserves broader consideration: its pain alleviating impact occurs in 90% of investigators” described the difference of real-time maximum insertion pain among WE, WI and AICD in clinical practice. We think it is useful to analyze the pain level in different medias and methods while colonoscopy in order to reduce the suffering of patient. It is a meaningful research in clinical practice. There was a logical design in methods and credible results.

**Answer:** Thank you for your supportive comments.

2. We still some suggestion about this paper despite your good writing. The English needs polishing especially in some detail.

**Answer:** The revised manuscript has been appropriately polished.

3. In discussion part, the description about the reason of inconsistent results of Investigator No 8 should be simplified.

**Answer:** We have summarized that part of discussion, simplifying the presentation of the causes of higher real-time insertion pain in the WE group of Investigator number 8. References have been changed accordingly.

Deleted From the manuscript (page 11, lines 15-29):

~~Factors that contributed to the aberrant findings of Investigator number 8, higher WE group real-time maximum insertion pain score compared with WI and AICD groups, were a significantly~~

~~higher proportion of patients, mostly females, that underwent colonoscopy for IBS or who had previous abdominal surgery. Patients undergoing colonoscopy for abdominal pain<sup>[11]</sup> and IBS as indication show significantly higher pain score during examination compared with non-IBS patients<sup>[11-16]</sup>. Female sex is considered to be a strong risk factor for pain during colonoscopy<sup>[1,12,13,17-19]</sup>, with expected difficult intubation and increased need for sedation<sup>[11,20,21]</sup>. The female pelvis is deeper and more rounded than its male counterpart and this may predispose to loop formation, particularly in the sigmoid colon<sup>[10]</sup>. Females tend to be less muscular than males, and their abdominal walls may provide less resistance and thus be less efficacious in counteracting colonoscope looping than males<sup>[20]</sup>. Moreover, women seem to have a longer transverse colon<sup>[20]</sup>. In female patients previous abdominal surgery is another factor associated with higher pain score<sup>[18,12,11,22]</sup> or with difficult colonoscopy<sup>[23]</sup>.~~

Inserted in the manuscript (page 12, lines 22-28):

Several factors contributed to the aberrant finding of Investigator's number 8 higher real-time maximum insertion pain score in the WE group compared with the WI and AICD groups: his WE group had a significantly higher proportion of female patients with abdominal pain as indication (this cohort comprised IBS cases) and with previous abdominal surgery. All these are risk factors for difficult or painful colonoscopy, with expected laborious intubation and increased need for sedation.

4. The analysis of the difference of pain among WE, WI and AICD should more detailed.

**Answer:** We present additional analyses of the study groups. They are presented as Supplementary Tables 1-3. Age (Supplementary table 1) and female sex (Supplementary Table 3) were comparable among groups and individual Investigators.

Indications for colonoscopy are reported in Supplementary Table 2. Abdominal pain had comparable proportions among methods and individual Investigators, except for Investigator number 1 and Investigator number 8 that had a significantly higher proportions in the WE group. This significant difference did not influence Investigator number 1 real-time insertion pain score in the WE group because, contrary to Investigator number 8 that as reported in the manuscript had also a significantly higher incidence of female patients with abdominal pain as indication and with previous abdominal surgery, Investigator number 1 had (WE, WI, AICD) 4:3:2 patients with those characteristics, more evenly distributed among the three groups, as reported in the table below.

Investigator number 1, differences associated with increase in real-time maximum insertion pain score among methods.

	<b>WE</b> <b>(n = 43)</b>	<b>WI</b> <b>(n = 37)</b>	<b>AICD</b> <b>(n = 43)</b>	<b>P value</b>
Females with abdominal pain as indication and previous abdominal surgery, n (%)	4 (9.3)	3 (8.1)	2 (4.7)	0.377 <sup>‡</sup> WE vs WI 1 WE vs AI 0.676 <sup>†</sup> WI vs AI 0.658 <sup>†</sup>

<sup>‡</sup> ANOVA, analysis of variance; <sup>†</sup> chi squared.

Regarding Bleeding, Change in bowel habits, Anemia, Others and Screening (all indications not associated with painful colonoscopy) there were no significant or clinically relevant differences among methods; differences within groups were likely due to clinical variations, as normally expected in clinical practice (Supplementary Table 2). Diverticulosis (indication associated with painful colonoscopy) was comparable among and within groups.

Supplementary Table 3 is a detailed report of the variations among the three study groups and individual Investigators of the data shown in Table 2 of the manuscript.

As already said female patients were equally distributed among and within the three study groups. BMI was comparable for each individual Investigator (except for Investigator number 9) and within the AICD group, as well as previous abdominal surgery (Supplementary table 3). These two items showed significant differences within the WE and the WI groups, as normally expected in clinical practice. WE showed the highest proportion of patients with previous abdominal surgery, factor associated with painful colonoscopy; however, WE achieved the lowest real-time insertion pain scores.

Within the study groups there were significant differences among the 10 individual Investigators in terms of use of abdominal compression, loop reduction and cecal intubation time (Supplementary Table 3), as already reported in the manuscript only for the WE group (Table 2).

We have reorganized data presentation in Table 2 of the manuscript and added Supplementary Tables 1-3, showing for all the study groups and individual Investigators patients' age, indications and differences relative to the issues reported in Table 2.

Added to the main body of text, in section Results (page 10, lines 4-16):

In greater detail, Supplementary Table 1 shows that age was comparable among the study groups and individual investigators. Indications for colonoscopy are reported in Supplementary Table 2. Abdominal pain had comparable proportions among methods and individual investigators, except for Investigator number 1 and Investigator number 8 that had significantly higher proportions in the WE group. The other indications were comparable among methods, except for Anemia (0.048).

Supplementary Table 3 shows that female patients were equally distributed among study groups and individual Investigators. There were significant differences in terms of BMI within the WE and WI groups ( $P = 0.025$  and  $P < 0.0005$ , respectively). The AICD group had the lowest proportion of patients with previous abdominal surgery, comparable among individual investigators ( $P = 0.405$ ). Among the 10 individual investigators there were significant differences in terms of use of abdominal compression, loop reduction and cecal intubation time.

Added to the main body of text 8, in section Discussion (page 12, lines 11-17):

Previous abdominal surgery is associated with higher colonoscopy pain score or with difficult procedures. The AICD group showed the lowest proportion of patients with previous abdominal surgery and had comparable BMI values among individual investigators (Supplementary Table 3); nevertheless, AICD pain scores were almost invariably higher than the other two groups (Table 2). Compared with WE, WI had a lower proportion of patients with previous abdominal surgery; and yet also WI showed a trend toward higher pain scores than WE (Table 2).

Reviewer # 43117

1. Authors have published a very similar manuscript at the CGH, May 2015. From the results and conclusion of this manuscript, we're not able to get new idea than the previous publication.

**Answer:** The new information in current study is the analysis of the performance of individual investigators. The CGH paper did not analyze or discuss individual colonoscopist's performance: in the article individual investigators' performances were lumped in a single study group (e.g. overall pain score of the WE, WI, AI or CO<sub>2</sub> groups).

In the current study we assessed the performance of individual investigators in decreasing colonoscopy real-time insertion pain to determine whether observations were reproducible across investigators and procedural factors contributing to variations, showing the high repeatability and reproducibility of WE in equalizing differences in real-time pain among colonoscopists.

2. How the patients were randomized?

**Answer:** added to the manuscript (page 7, lines 20-23):

Enrolled patients were assigned to the different insertion techniques by computer-generated lists, with block allocation and stratification based on participating endoscopists. Group assignment was kept in sealed envelopes that were opened just before the start of the procedure.

3a. At table 5, it is not reasonable that all the patients were unsedated, there should be a group of patients received midazolam for sedation.

**Answer:** We report here Table 5 for discussing issues 3a and 3b.

Table 5: Pain during insertion, patients' tolerance and sedation.

	<b>WE</b> <i>N</i> = 371	<b>WI,</b> <i>N</i> = 338	<b>AICD</b> <i>N</i> = 382	<b><i>P</i> value</b>
Painless unsedated colonoscopy, ** <i>n</i> (%)	50 (13.5)	26 (7.7)	23 (6.0)	WE vs WI 0.013 <sup>†</sup> WE vs AICD < 0.0005 <sup>†</sup> WI vs AICD 0.374 <sup>†</sup>
Unsedated, completed with only discomfort, ** <i>n</i> (%)	134 (36.1)	106 (31.4)	87 (22.8)	WE vs WI 0.180 <sup>†</sup> WE vs AICD < 0.0005 <sup>†</sup> WI vs AICD 0.009 <sup>†</sup>
Completed without sedation, <i>n</i> (%)	321 (86.5)	287 (84.9)	292 (76.4)	WE vs WI 0.537 <sup>†</sup> WE vs AICD < 0.0005 <sup>†</sup> WI vs AICD 0.004 <sup>†</sup>

\*\* Pain score based on numeric rating scale (NRS): 0=absence of pain, 1-2=discomfort, 10=maximum pain.

In the manuscript we already reported the proportions of patients completing the procedure without sedation (row number 4, highlighted in green).

Subtracting from the total number of patients in each group the number of patients completing the procedure without sedation, one obtains the number of the patients that requested sedation. For example, WE *n* = 371 - 321 = 50 unsedated patients. The same holds true for the WI and AICD groups. Of course, the *P* values are identical. We thought that this information was redundant.

As requested, we added a row (number 5) to Table 5 (page 25), highlighted below:

	<b>WE</b> <i>N</i> = 371	<b>WI,</b> <i>N</i> = 338	<b>AICD</b> <i>N</i> = 382	<b><i>P</i> value</b>
<b>On-demand sedation, <i>n</i></b> <b>(%)</b>	<b>50 (13.5)</b>	<b>51 (15.1)</b>	<b>90 (23.6)</b>	<b>WE vs WI 0.537<sup>†</sup></b> <b>WE vs AICD &lt; 0.0005<sup>†</sup></b> <b>WI vs AICD 0.004<sup>†</sup></b>

Presentation of these data (page 11, lines 25-27) has been inserted in the manuscript:

Accordingly, WE and WI showed low proportions of patients requesting on-demand sedation: WE 13.5%, vs WI 15.1% ( $P = 0.537$ ); vs AICD 23.6% ( $P < 0.0005$ ); WI vs AICD  $P = 0.004$  (Table 5).

3b. More interesting and important question is that how is the proportion of patient that could omit the sedation.

**Answer:** The proportion of patients not receiving sedation was already reported in row number 4 of Table 5 (now highlighted in green), reported above.

4. In addition to the maximal real time pain in insertion, readers would also like to know the post-CFS (recovery stage) discomfort? Is there any difference among these procedures?

**Answer:** We have no data about post-colonoscopy discomfort or pain. Thank you for the suggestion, that will be the focus of one of our future studies.