COMMENTARY
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Carbon Dioxide Insufflation in Endoscopic Submucosal Dissection: Is It an Urgent Need?

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See "Carbon Dioxide versus Air Insufflation in Gastric Endoscopic Submucosal Dissection: A Systematic Review and Meta-Analysis of Randomized Controlled Trials" by Ramkaji Baniya, Sunil Upadhaya, Jahangir Khan, et al., on page 464-472.

Endoscopic submucosal dissection (ESD) is a standard treatment for patients with gastrointestinal neoplasm who have a negligible risk of lymph node metastasis.[1,2] ESD enables *en bloc* resection of gastrointestinal neoplasm and organ preservation, thus, avoiding surgical treatment.

With the advances in endoscopic skills and expertise, endoscopists have focused on ensuring the quality of recovery of patients as well as reducing procedure-related adverse events such as gastric perforation, hemorrhage, or abdominal pain.

Procedure-related gastric perforation or hemorrhage might be less significant, because it is usually managed by endoscopic hemostasis or clipping without additional surgical treatments in skilled endoscopies. However, procedure-related abdominal pain or discomfort might lower the quality of recovery of patients after gastric ESD.

Distension of the intestinal lumen is essential to ensure adequate visibility and to secure the space required for a safe procedure.[3] During endoscopic procedures, a large amount of gas is insufflated (i.e., 8–18 L during diagnostic colonoscopy, which far exceeds the physiological gastrointestinal gas with a volume of 0.1–1 L).[4-6]

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Room air is the most commonly used material during diagnostic and therapeutic endoscopic procedures. However, it can cause abdominal pain, because it is poorly absorbed in the intestines and is mostly excreted by belching or passage of flatus.[3] Moreover, abdominal discomfort or pain due to retained gas is common. When gastric perforation occurs, the leaked air increases the intra-abdominal pressure and can induce pneumoperitoneum. Although rarely observed, air embolism is another adverse event related to ESD-induced gastric perforation.[7-9] To overcome these potentially fatal adverse events, carbon dioxide (CO_2) instead of room air has been proposed as the insufflating agent, because CO_2 is rapidly absorbed by tissues.[3]

CO_2 was proposed as the insufflating agent of the large intestine in the 1950s, and it has been used to distend the abdominal cavity for endoscopic exploration of the peritoneal cavity during laparoscopic surgery.[10] CO_2 is 160 times more rapidly absorbed than nitrogen is and 13 times more rapidly absorbed than oxygen is.[3,6,11] It is passively absorbed through the gastrointestinal mucosa into the bloodstream and is eventually exhaled through the lungs.[6] Therefore, rapid absorption of CO_2 can minimize the barotrauma and can rapidly reduce luminal distension.[3] The superior efficacy of CO_2 (vs. room air) in reducing postoperative pain or discomfort during laparoscopic surgery has been established.[11] However, this has not been extensively evaluated in the field of gastric ESD.

In a recent issue of *Clinical Endoscopy*, Baniya et al. reported a systematic review and meta-analysis of CO_2 vs. room air insufflation in gastric ESD focusing on post-procedural abdominal pain and adverse events.[12] Unlike a recently published

meta-analyses[11] about the efficacy and safety of CO_2 (vs. room air) insufflation in ESD (combining gastric, colorectal, and esophageal ESD), this study[12] focused only on gastric ESD. Therefore, readers can understand the results of this study under the scope of subgroup analysis of the study by Li et al., although this analysis was not conducted in their study.[11]

Although the meta-analyses by Li et al.[11] and Baniya et al.[12] commonly claimed less post-procedural abdominal pain or discomfort in the CO_2 insufflation group (vs. room air insufflation) of patients with ESD[11] or those with gastric ESD,[12] they could not overcome the methodological limitations. When the enrolled studies report multiple outcomes, it is difficult to select the optimal value for the meta-analysis. Several methods have been proposed to select the representative outcome of studies with multiple outcomes. Averaging the reported values and setting them as a representative value (shifting unit of analysis for subgroup analysis) or selection of one most clinically representative value are typically practiced.[13]

In the meta-analysis by Baniya et al.,[12] the values of three studies (studies by Tanioka et al.,[14] Maeda et al.,[15] and Kim et al.[16]) were combined (Table 3 and Fig. 2 in their study[12]), while Tanioka et al.[14] presented only one value (abdominal pain after gastric ESD on a 100-mm visual analogue scale), namely 14.3±20.5 (CO_2 group) vs. 24.3±25.3 (air group). Maeda et al.[15] and Kim et al.[16] presented four values in each study. Therefore, an optimal value should be selected for the meta-analysis in the studies by Maeda et al.[15] and Kim et al.[16] Baniya et al. selected maximal post-procedure abdominal pain as the primary effect size to combine.[12] Therefore, the values 14.3±20.5 (CO_2 group) vs. 24.3±25.3 (air group) in the study by Tanioka et al.[14] and 35.2±30.3 (CO_2 group) vs. 48.5±29 (air group) in the study by Kim et al.[16] were selected for the meta-analysis (Table 3 in their study[12]). However, 1 (CO_2 group) vs. 4 (air group) in the study by Maeda et al.[15] were selected instead of 4 (CO_2 group) vs. 4 (air group), which are the maximal values.[12] Moreover, the pain level during the first hour after the procedure was the highest in all three studies; however, Baniya et al.[12] selected only the value observed the next day of the procedure reported in a study by Maeda et al.[15] Considering the 4 (CO_2 group) vs. 4 (air group), which are the maximal values during the first hour after the procedure in the study by Maeda et al.,[15] it is reasonable to choose these values. If these values were used for meta-analysis, the result would be no longer significant.

A recently published meta-analysis by Li et al.[11] also claimed less significant post-ESD abdominal discomfort in the CO_2 insufflation group (vs. room air insufflation). However, they did not perform subgroup analysis to distinguish between the esophagus, stomach, and colon ESD to evaluate whether they could achieve the expected results. Owing to the differences in database selection and inclusion criteria, there was a discrepancy in the enrolled studies on gastric ESD from the study by Baniya et al.;[12] this is another limitation of this method.

Despite its theoretical safety, the superior recovery quality of CO_2 insufflation (vs. room air insufflation) is uncertain in various endoscopic procedures, except for colonoscopy.[17] In addition, the superior recovery quality of CO_2 insufflation might not be applicable in gastric ESD, because most of the insufflated agents are excreted by belching or endoscopic suction immediately after a certain amount of air is accumulated in the stomach. Therefore, the influence of insufflated agents might be less significant than that of colonoscopy on abdominal discomfort. Moreover, abdominal discomfort does not depend entirely on the use of insufflated agents, but is also associated with the sedation level of the patient. This was not measurable in this study. ESD-induced iatrogenic ulcer itself can cause abdominal discomfort regardless of the insufflating agents used. The implications of this study are also alleviated, because allocation concealment of enrolled studies, which is the key factor of randomized studies, was not performed or measurable throughout the enrolled studies.

Considering the factors stated above, CO_2 insufflation may offer advantages over air insufflation with respect to unexpected serious complications of ESD, especially in gastric perforation. However, it is not an urgent need for relief of abdominal pain or discomfort in gastric ESD, especially for skilled endoscopists.

Conflicts of Interest

The authors have no financial conflicts of interest.

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