Efficacy of carbon dioxide insufflation during gastric endoscopic submucosal dissection: a randomized, double-blind, controlled, prospective study

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Background and Aims: Endoscopic submucosal dissection (ESD) is commonly performed under air insufflation and is often accompanied by abdominal discomfort. CO_2 is absorbed more rapidly by the body than is air; however, the use of CO_2 insufflation in ESD remains controversial. This randomized, double-blind, controlled, prospective study was designed to assess the efficacy of CO_2 versus air insufflation in gastric ESD.

Methods: Between May 2012 and August 2014, a total of 110 patients with gastric tumors were randomly assigned to the CO_2 insufflation (CO_2 group, n = 54) or air insufflation group (air group, n = 56). Abdominal pain after ESD was chronologically recorded via visual analog scale (VAS) scores. Secondary outcome measurements were adverse events, abdominal circumference, amount of sedatives prescribed, and use of analgesics.

Results: Neither the baseline patient characteristics nor the mean procedural time differed between the groups. The VAS score for abdominal pain was 35.2 in the CO_2 insufflation group versus 48.5 in the air insufflation group 1 hour after ESD ($P = .026$), 27.8 versus 42.5 three hours after ESD ($P = .007$), 18.4 versus 34.8 six hours after ESD ($P = .001$), and 9.2 versus 21.9 one day after ESD ($P < .001$). Changes in abdominal circumference, the amounts of sedative drugs taken, and the adverse events did not differ between the groups. However, the air insufflation group required more analgesics than did the CO_2 insufflation group (CO_2 group, 22.0% [11/50]; air group, 42.3% [22/52]; $P = .028$).

Conclusions: CO_2 insufflation during gastric ESD significantly reduced abdominal pain and analgesic usage compared with air insufflation. (Clinical trial registration number: NCT01579071.) (Gastrointest Endosc 2015;82:1018-24.)

Endoscopic submucosal dissection (ESD) is a new treatment for early stage cancer of the digestive tract.[1] Insufflation is required during ESD to allow adequate visualization of the gut lumen. To date, it has been standard practice to insufflate the lumen with room air. However, a high volume of insufflated gas can distend the gut, causing postprocedural pain and discomfort.[2] Unlike air, CO_2 is rapidly absorbed by the intestinal mucosa and subsequently expired via the lung, possibly decreasing the duration of bowel distension.[3]

In several studies, CO_2 insufflation reduced procedure-related pain and discomfort.[2,4-9] CO_2 insufflation also would be expected to help maintain a stable hemodynamic state and respiration during ESD because CO_2 insufflation may restrict the increase in inner pressure of the GI tract as a result of quick absorption into the bloodstream.[3,10-12] Pneumoperitoneum or mediastinal emphysema resulting from CO_2 insufflation also may disappear quickly because leaking CO_2 in the peritoneal cavity or mediastinum is rapidly absorbed into the bloodstream.[3,10-12] The safety of CO_2 insufflation during ESD has been demonstrated in several studies.[13,14] As an alternative to air, CO_2 has been insufflated effectively during colorectal and esophageal

Abbreviations: ESD, endoscopic submucosal dissection; RCT, randomized controlled trial; VAS, visual analog scale.

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ESD.[13,15,16] Although many studies on the efficacy of CO_2 insufflation during endoscopy have thus appeared, trials of the efficacy of such insufflation during gastric ESD are few in number. To the best of our knowledge, only a single relevant randomized controlled trial (RCT) has been performed.[17] Thus, we conducted a prospective, double-blind, RCT to assess the efficacy of CO_2 insufflation in patients undergoing gastric ESD.

PATIENTS AND METHODS

Patients

All patients provided written informed consent before gastric ESD. Between May 2012 and August 2014, all consecutive patients undergoing gastric ESD at the Gil Medical Center were screened. The exclusion criteria were as follows: chronic obstructive pulmonary disease with retention of CO_2, heart failure with dyspnea, an inability to complete the relevant questionnaire, and refusal to participate. We informed all patients of our aims, methods, and the possible side effects and obtained signed written consents from all. The study was approved by the Institutional Review Board of the Gil Medical Center (IRB No. GIRBA 2681-2012) and was registered in the clinical trial database at http://www.clinicaltrials.gov (NCT01579071).

Blinding and endoscopic procedure

This was a single-center, double-blind, prospective, RCT. Participants were allocated randomly to either the CO_2 insufflation (CO_2) or air insufflation (air) group, by using a randomization schedule generated by using http://www.randomization.com by an investigator not involved in the work. All endoscopists, patients, and recovery room nurses were blinded to the gas used. A nursing assistant operated the CO_2 device ("on" and "off") as dictated by the randomization. The gas equipment was hidden from the endoscopist by draping and was retained in the endoscopy unit even when not in use.

ESD was performed with the aid of a GIF-Q260 or GIF-Q260J endoscope (Olympus Medical Systems Corp, Tokyo, Japan); a transparent hood (D-201-10704; Olympus Medical Systems Corp) was attached to the tip of either endoscope. A water-jet junction or a hand-made external water channel was used during ESD, which featured the use of flex, an insulation-tipped knife (IT2; Olympus Medical Systems Corp, Tokyo, Japan), and dual knives. Sodium hyaluronate (Endo-MucoUp 20, BMI Korea Corp, Uiwang, Korea) was locally injected into the submucosa. The electrocautery unit (VIO 300 D; ERBE, Tübingen, Germany) was operated in the endo-cut mode (effect 2; cut duration 2; cut interval 2) running the 40 W swift-coagulation option. All ESD procedures were performed by 5 endoscopists, each of whom had at least 5 years of experience in therapeutic GI endoscopy. All procedures were performed on an inpatient basis.

CO_2 insufflation and intraprocedural management

CO_2 was administered with the aid of a commercial CO_2-efficient endoscopic insufflator (Colosence Pro-500; Miraemedics Inc, Sung Nam, Korea) connected to a CO_2 bottle. Oxygen saturation, blood pressure, and heart rate were monitored constantly.

A combination of propofol and midazolam (given as an intravenous bolus) was used for sedation. After an appropriate sedation level had been attained, continuous drip infusion (1-5 mg/kg/h) of propofol, via a syringe pump, was used to preserve sedation. The volume of oxygen inhaled and the rate of intracellular fluid infusion were increased if cardiopulmonary repression developed, and the rate of propofol infusion was reduced under such circumstances. The target sedation level was moderate to deep. Clinical sedation states were defined by using the practice guidelines of the American Society of Anesthesiologists Task Force.[18]

Postprocedural management

All patients fasted on the day of ESD and the following day. Chest and abdominal radiographs were obtained immediately after ESD and perforations sought. Laboratory tests were run before ESD and on day 1 thereafter. After ESD, analgesics (tramadol; Tridol, Yuhan Corporation, Seoul, Korea; or diclofenac; Dicknol, Myungmoon Pharmaceuticals, Seoul, Korea) were prescribed if any patient complained of severe pain. The day after the procedure, follow-up upper GI endoscopy was performed to search for post-ESD lesions. If any procedural adverse event developed, endoscopic treatment was performed.

Study endpoints and outcome measurements

The primary endpoint of the study was the severity of abdominal pain, as recorded on a 100-mm visual analog scale (VAS) 1 hour after ESD. The 100-mm VAS ranged from "no pain" on the left to "pain as bad as it could be" on the right. Abdominal pain estimates were taken 1, 3, 6, and 24 hours after ESD.

The secondary endpoints were abdominal distention (waist circumference was measured at the start of the procedure and immediately thereafter by using a tape measure), the amounts of sedative drugs (propofol and midazolam) and analgesics prescribed, and adverse events.

Sample size and statistical analysis

The required sample size was estimated via prospective power analysis. Sample size calculation was based on between-group VAS score differences 1 hour after the procedure. By using data available at the time of study planning,[4,5,8,19,20] we estimated that the air group would have a mean VAS score of 40 mm and the CO_2 group a mean score of 20 mm. Thus, each group had to include 45