Carbon dioxide insufflation reduces the discomfort due to colonoscopy as objectively analyzed by salivary stress markers

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Abstract

Background : **Carbon dioxide (CO_2) insufflation has been shown to reduce the procedure-related pain and discomfort during colonoscopy. However, the effects of CO_2 insufflation on the improvement of participant's stress had not been objectively analyzed.**

Methods : **Using a randomized, double-blinded design, 100 consecutive patients undergoing colonoscopy were assigned to have their examination performed with either CO_2 or air insufflation. Patients completed a questionnaire to grade their discomfort using a visual analogue scale (VAS). The salivary alpha-amylase (SAA) level was also measured at these times as a marker of stress.**

Results : **The total VAS score did not show any statistically significant differences between the CO_2 and air insufflation groups. However, the VAS score for abdominal fullness significantly decreased in the CO_2 insufflation group in comparison to the air insufflation group in the patients who had a longer examination. The titer of the maximum SAA was significantly increased by colonoscopy ($P < 0.01$). CO_2 insufflation significantly reduced the total SAA after the colonoscopy in comparison with air insufflation ($P < 0.05$). The examination time and SAA tended to have a positive relationship in the air insufflation group. However, no such relationship was observed in the CO_2 insufflation group.**

Conclusions : **CO_2 insufflation significantly reduced the post-examination discomfort, as indicated by a salivary stress marker. The use of CO_2 rather than air insufflation reduced the patients' stress and may contribute to better acceptance of colonoscopy. The usefulness of CO_2 insufflation was more prominent when a longer examination was necessary.** (Acta gastroenterol. belg., **2013**, 76, **219-224**).

Key words : carbon dioxide insufflation, colonoscopy, stress, visual analogue scale, salivary alpha-amylase.

Introduction

Colonoscopy is widely used as a screening or therapeutic tool for colorectal diseases (1,2). However, colonoscopy sometimes has the disadvantage of inducing abdominal pain and discomfort for patients (3). During endoscopy, air is commonly used to insufflate the bowel to observe the lumen. This insufflation of air during colonoscopy is one of the reasons for the occurrence of abdominal pain, fullness and discomfort for patients. As a result, some innovations concerning endoscopic tools were developed to try to reduce the patients' discomfort during colonoscopy. The use of carbon dioxide insufflation instead of air insufflation was one of these innovations. Because carbon dioxide is rapidly absorbed and excreted through the lungs, the abdominal fullness and discomfort for patients may be reduced. Indeed, the use of carbon dioxide rather than air insufflation has been shown to reduce the procedure-related pain and discomfort associated with colonoscopy (4-7). As a result, carbon dioxide alleviates post-colonoscopy discomfort. Moreover, it has been shown that the use of carbon dioxide during colonoscopy has no adverse effects (4-7). Recently, carbon dioxide insufflation has also been considered for lengthy endoscopic treatments, such as endoscopic submucosal dissection (ESD) (8).

Many reports have shown the usefulness of carbon dioxide insufflation (4-10). For example, Stevenson *et al* (9) showed a significant reduction of gas distention in the large and small bowel by abdominal radiography in the carbon dioxide insufflation group. Another group showed the usefulness of carbon dioxide insufflation by using a visual analog scale (VAS) or questionnaire for patients (10,11). Therefore, carbon dioxide insufflation may be useful to reduce the patients' stress due to abdominal pain, fullness and the discomfort of the colonoscopy. However, the effects of carbon dioxide insufflation on the improvement of patients' stress have not been objectively analyzed in any of the previous studies. A VAS or questionnaire for patients was usually used for such assessments. However, the results obtained using these methods depend on the patients' characteristics and are often subjective.

Recently, it was demonstrated that monitoring the salivary alpha-amylase (SAA) level could be used to objectively assess psychological stress (12-16). SAA, alpha-1,4-alpha-d-glucan 4-glucanohydrolase, is one of the most important enzymes present in saliva (15,16). It consists of two families of isoenzymes, one of which is glycosylated, while the other contains no carbohydrate.

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Satoru Kakizaki ; analysis and interpretation of data, drafting the article.
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SAA is a calcium-containing metalloenzyme that hydrolyzes the alpha-1,4 linkages of starch to glucose and maltose. It is known to be mainly involved in the initiation of the digestion of starch in the oral cavity. However, it was showed that the autonomic nervous system plays a powerful role in the secretion of SAA, with contributions by both the alpha-adrenergic and the beta-adrenergic mechanisms (15-18). As a result, SAA might be regarded as an indirect indicator of autonomic activation. The primary peripheral systems that are activated in response to psychological stressors are the hypothalamic – pituitary – adrenal (HPA) axis and the autonomic nervous system, which includes both the sympathetic and parasympathetic nervous systems. Until the development of the SAA method, peripheral biomarkers reflecting autonomic activity had been lacking. SAA has also recently emerged as a surrogate marker of sympathetic nervous system activity (15). Although SAA is not a direct product of the sympathetic nervous system, there have been several studies showing the involvement of the autonomic nervous system, particularly its sympathetic branch, in the secretion of SAA (15).

In this study, we evaluated the efficacy of carbon dioxide insufflation on improving a participant's stress after colonoscopy by an objective method using SAA measurements. The stress levels of patients were analyzed both objectively by the SAA method and using a conventional VAS method. Carbon dioxide insufflation for colonoscopy showed efficacy in the reducing the patients' stress both in the VAS and objectively based on the stress marker method.

Patients and Methods

Study population

Consecutive patients aged 30-65 years who were scheduled for colonoscopy at Maebashi Red Cross Hospital were included in this study. Patients with the following clinical features were excluded : presence of significant comorbidities ; presence of bowel obstruction or stenosis ; known allergy to polyethylene glycol (PEG)-electrolyte solution ; history of gastric, colonic or gynecological surgery ; pregnancy ; irritable bowel syndrome or inflammatory bowel diseases or chronic respiratory diseases. A gastroenterologist assessed the patient eligibility, and written informed consent was obtained from each patient. Patients were randomly allocated to undergo colonoscopy with carbon dioxide insufflation or air insufflation. The patients were blinded with regard to the type of gas used. This was a randomized, prospective, open-labeled study, and was reviewed and approved by the ethics committee of Maebashi Red Cross Hospital.

Endoscopy and carbon dioxide insufflation

The bowel preparation regimens and schedule for experiments were as follows : The day before colonoscopy, all patients were administered 24 mg of Sennoside (Novartis Pharma K.K. Tokyo, Japan) at 9:00 p.m. On the day of the colonoscopy, all participants came to the endoscopy room, and received an in-hospital bowel preparation. Because we employed this in-hospital preparation, uniformity of procedures within the study was achieved. All patients were on the same time schedules, which reduced the influence of circadian changes in the SAA level. Participants started to drink the 2000 mL of PEG-electrolyte solution at 9:30 a.m.

Carbon dioxide was administered using a commercially available carbon dioxide regulator designed for use in endoscopy procedures, OLYMPUS UCR (Olympus Co. Ltd., Tokyo, Japan), which was connected to a carbon dioxide bottle. Procedures were performed using an Olympus CF-240 or CF-Q260AI colonoscope (Olympus Co. Ltd., Tokyo, Japan). All examinations were performed using 10 mg of intramuscular scopolamine butylbromide as an antispasmodic without sedatives or analgesics by three blinded endoscopists who had over 10 years of endoscopy experience. Participants who were contraindicated for scopolamine butylbromide were excluded from the study. The length of the examination was considered to be the time required to complete the colonoscopy.

Evaluation of abdominal discomfort

A questionnaire with a visual analog scale (VAS) was used to quantify the abdominal discomfort (abdominal fullness, pain, and nausea) experienced before and after finishing the examination (just after the examination and 30 minutes and 1 hour after the examination). The VAS used ranged from "no symptoms" on the far left to "representing the worst symptoms imaginable" on the far right. The scale was 7 cm in length, and the distance in centimeters from 0 to the line indicating the severity of symptoms experienced was measured. VAS scores were calculated for all three categories. A total VAS score was calculated as the sum of the three categories.

Salivary alpha-amylase (SAA) as a stress marker

As a stress marker, the salivary alpha-amylase (SAA) level was measured. Saliva was collected pre-procedure, and immediately, 30 minutes and 60 minutes after the colonoscopy using a previously reported method (17). The samples were frozen at –20°C from the completion of the session until the analyses took place. The concentration of SAA was measured by an enzyme kinetic method according to the protocol specified by Rohleder *et al*. (18).

Statistical analyses

The data were expressed as the means ± SD. The data were analyzed using the Fisher's exact probability test, an analysis of variance (ANOVA) and Tukey-Kramer post hoc tests. A Spearman correlation coefficient obtained by the log rank test was used to evaluate the relationships between the SAA, VAS score and

Table 1. — **Characteristics of the patients with carbon dioxide and air insufflation groups**

		Carbon dioxide insufflation	Air insufflation	P value
Number of patients		47	50	
Age	years	58.9 ± 10.8	56.6 ± 12.2	N.S.
Sex	male/female	36/11	38/12	N.S.
Body Mass Index	kg/m^2	22.5 ± 2.6	23.1 ± 2.8	N.S.
Length of the examination	min	21.0 ± 12.0	19.9 ± 9.1	N.S.
Common use of laxative	yes/no	4/43	3/47	N.S.

length of the procedure. A value of $P < 0.05$ was considered to be significant.

Results

Patient characteristics and colonoscopy

A total of 100 patients were examined. Three patients were excluded due to the presence of exclusion criteria or uncompleted questionnaires. Therefore, the data for 97 patients were analyzed in this study. There were 47 patients in the carbon dioxide group, and 50 patients in the air group. The baseline characteristics of the patients in both groups are shown in Table 1. There were no significant differences in the patient age, sex, body mass index, length of the examination, or use of laxatives between the carbon dioxide and control groups.

Measurements of abdominal discomfort by a visual analog scale (VAS)

Before the examination, there were no differences in the mean VAS scores in terms of the overall score or the scores for abdominal fullness, pain, and nausea between the carbon dioxide and control groups (Table 2). The overall VAS score and the VAS scores for abdominal fullness and pain were significantly increased after the colonoscopy ($P < 0.01$). However, the VAS score for nausea was not increased after colonoscopy. In the carbon dioxide group, the total VAS score and the scores for abdominal fullness and pain recovered to the basal level by 30 minutes after the colonoscopy. However, the VAS scores continued to increase at 30 minutes in the air insufflation group ($P < 0.01$).

The mean total length of the colonoscopy was 21.0 ± 12.0 min in the carbon dioxide group and 19.9 ± 9.1 min in the air insufflation group. The length of the examination was not significantly different between the two groups. Eighteen of the 47 patients in the carbon dioxide group underwent a procedure that lasted more than 20 minutes, while 20 of 50 patients in the air insufflation group underwent procedures that lasted longer than 20 minutes. The incidence of the examinations taking more than 20 minutes was not significantly different between the carbon dioxide and air insufflation groups. Table 3 shows the VAS for abdominal discomfort between carbon dioxide and air insufflation in the patients whose procedures lasted more than 20 minutes. As was the case with the total patient cohort, the total VAS score and VAS scores for abdominal fullness and pain increased after colonoscopy. However, statistically significant differences were only observed in the air insufflation group. This may have been due to the smaller numbers of patients in this group in comparison to the total number of patients (analyzed in Table 2). However, the differences between carbon dioxide and air insufflation were more prominent in these patients who underwent procedures that lasted more than 20 minutes.

The VAS scores recovered to the basal level within 30 minutes after colonoscopy in the carbon dioxide group. However, the VAS scores continued to increase at 30 minutes in the air insufflation group. Of note, the total VAS score and VAS score for abdominal fullness tended to be lower in the carbon dioxide group at 30 minutes after the colonoscopy in comparison with air insufflation group. As a result, carbon dioxide insufflation reduced the procedure-related discomfort associated with colonoscopy in comparison to air insufflation. Carbon dioxide insufflation was especially effective in reducing the sensation of abdominal fullness in the patients who underwent longer examinations.

The effects on the salivary alpha-amylase (SAA) level as a stress marker

Before the examination, there were no significant differences in the mean SAA between the carbon dioxide group ($11.5 \pm 10.4 \times 10^4$ U/mL) and the air insufflation group ($13.9 \pm 12.5 \times 10^4$ U/mL, Figure 1). After colonoscopy, the SAA level tended to increase in both groups, although the increase did not reach the statistical significance. However, the maximum SAA levels at the three points after the procedure all significantly increased in both groups ($19.1 \pm 15.0 \times 10^4$ U/mL in the carbon dioxide and $26.7 \pm 20.1 \times 10^4$ U/mL in the air insufflation groups, respectively, $P < 0.01$ in comparison with the score before the procedure). The total SAA levels at the three points after the procedure were significantly increased in the air insufflation group ($50.2 \pm 33.8 \times 10^4$U/mL) in comparison with the carbon dioxide group ($40.0 \pm 31.4 \times 10^4$U/mL, $P < 0.05$).

To determine the relationship between the SAA, VAS score and length of the examination, a Spearman correlation coefficient determined by a log rank test was

Table 2. — **Visual analogue scales (VAS) for abdominal discomfort between carbon dioxide and air insufflation groups**

		Carbon dioxide insufflation	Air insufflation
Total VAS score	Before	4.0 ± 1.7	3.9 ± 1.9
	Just after	6.5 ± 3.3**	6.7 ± 3.5**
	After 30 min	5.3 ± 2.5	6.1 ± 3.5**
	After 60 min	4.6 ± 2.5	4.9 ± 2.9
Abdominal fullness	Before	1.6 ± 1.0	1.4 ± 0.8
	Just after	2.9 ± 1.7**	3.0 ± 1.9**
	After 30 min	2.3 ± 1.4	2.8 ± 1.9**
	After 60 min	2.0 ± 1.2	2.2 ± 1.5
Pain	Before	1.2 ± 0.6	1.3 ± 0.8
	Just after	2.4 ± 1.6**	2.5 ± 1.8**
	After 30 min	1.9 ± 1.1	2.1 ± 1.6*
	After 60 min	1.6 ± 0.9	1.6 ± 1.1
Nausea	Before	1.2 ± 0.6	1.2 ± 0.5
	Just after	1.2 ± 0.5	1.2 ± 0.6
	After 30 min	1.1 ± 0.3	1.2 ± 0.6
	After 60 min	1.0 ± 0.2	1.2 ± 0.6

** : $P < 0.01$, * ; $P < 0.05$ in comparison to the previous score.

Table 3. — **Visual analogue scales (VAS) for abdominal discomfort in the patients with over 20 min examination time**

		Carbon dioxide insufflation	Air insufflation
Total VAS score	Before	4.0 ± 1.7	3.9 ± 2.4
	Just after	6.3 ± 3.5	6.9 ± 3.7**
	After 30 min	4.8 ± 2.0	6.0 ± 2.8
	After 60 min	3.9 ± 1.3	4.8 ± 1.9
Abdominal fullness	Before	1.56 ± 1.0	1.4 ± 1.0
	Just after	2.8 ± 1.8	3.2 ± 1.0**
	After 30 min	2.0 ± 1.2	2.8 ± 1.7**
	After 60 min	1.5 ± 0.8	2.2 ± 1.3
Pain	Before	1.3 ± 0.5	1.3 ± 0.9
	Just after	2.3 ± 1.6	2.6 ± 1.9**
	After 30 min	1.8 ± 1.0	2.1 ± 1.4
	After 60 min	1.4 ± 0.6	1.6 ± 0.8
Nausea	Before	1.2 ± 0.5	1.2 ± 0.56
	Just after	1.2 ± 0.5	1.1 ± 0.3
	After 30 min	1.1 ± 0.2	1.1 ± 0.3
	After 60 min	1.0 ± 0.0	1.1 ± 0.3

** : $P < 0.01$, * ; $P < 0.05$ in comparison to the previous score.

used. There was no significant relationship between the VAS score and length of the examination. Although it did not reach statistical significance, there was a tendency for a positive relationship between the total SAA and length of the examination in the air insufflation group (Correlation coefficient 0.290, $P = 0.082$, Figure 2A). On the other hand, such relationships were not observed in the carbon dioxide insufflation group (Correlation coefficient -0.022, $P = 0.898$, Figure 2B). As a result, the discomfort in the carbon dioxide insufflation group was not influenced by the longer examination. On the other hand, the discomfort in the air insufflation group was influenced by the longer examination.

Discussion

This study showed that carbon dioxide insufflation was effective for reducing the patients' stress during and after colonoscopy. Furthermore, carbon dioxide insufflation was especially effective for reducing stress in the patients whose examinations lasted longer than 20 minutes. We showed these results by both the VAS and the SAA levels. Carbon dioxide, rather than air, insufflation has previously been shown to reduce procedure-related pain and discomfort in patients undergoing colonoscopy (4-7). These reports showed the usefulness of carbon dioxide insufflation by the VAS or a questionnaire (4-7). In the present study, the usefulness of carbon dioxide insufflation was shown by the VAS, as in previous reports. However, we also showed the effects of carbon dioxide insufflation on the improvement of the patients' stress objectively by monitoring the SAA levels.

Wang *et al*. (7) performed a meta-analysis and compared the air insufflation and carbon dioxide insufflation during colonoscopy. They showed that carbon dioxide insufflation causes lower post-procedural pain and bowel distension, without a significant pCO_2 variation. Imai *et al*. (6) evaluated the efficacy of carbon dioxide insufflation during colonoscopy in patients with irritable bowel syndrome (IBS). They showed that carbon dioxide

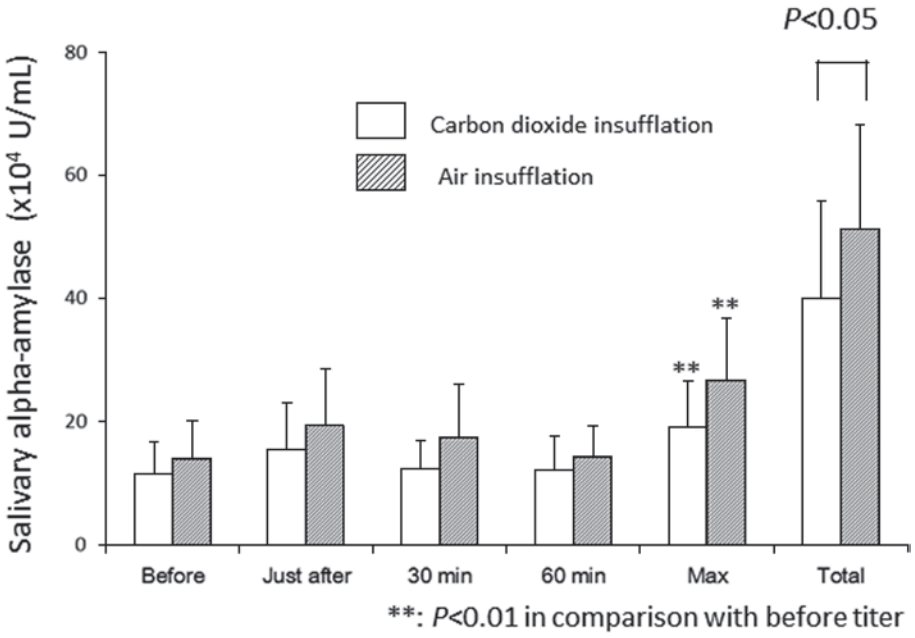

Fig. 1. — The changes and time courses of salivary alpha-amylase (SAA) levels between the carbon dioxide and air insufflation groups. Blank square ; Carbon dioxide insufflation group, Oblique lined square ; Air insufflation group.

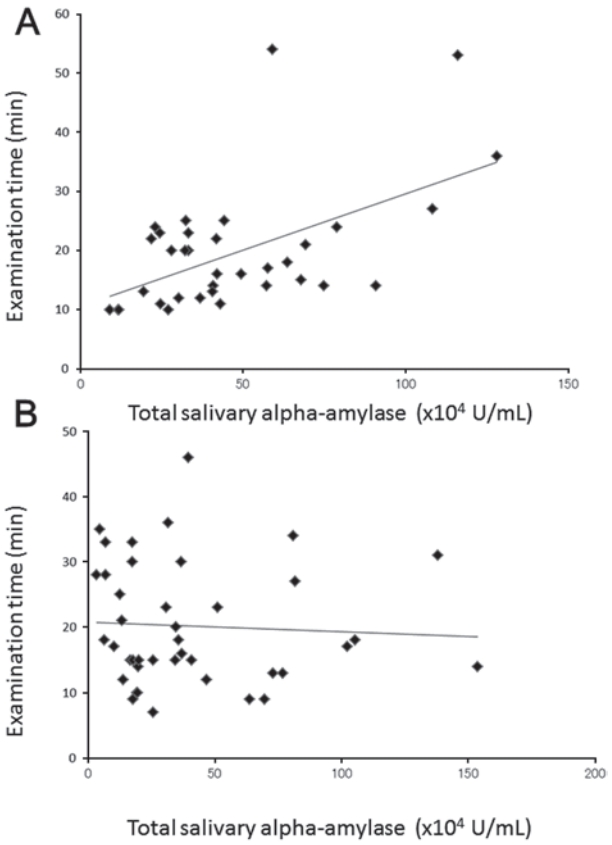

Fig. 2. — Correlation between the SAA level and length of the examination. A ; Air insufflation group, B ; Carbon dioxide insufflation group.

insufflation during colonoscopy was effective for IBS patients, particularly because patients could commence their activities after colonoscopy. Many studies have evaluated the usefulness of carbon dioxide insufflation during colonoscopy. However, the carbon dioxide insufflation has disadvantages concerning the cost-effectiveness and the system used to deliver the gas. Not all institutes have a carbon dioxide insufflation system, and carbon dioxide insufflation costs more than air insufflation.

In this study, we showed that carbon dioxide insufflation was especially effective in reducing stress in patients who underwent longer examinations. When carbon dioxide insufflation is difficult due to the cost, then patients who are expected to require longer examinations should be selected for carbon dioxide insufflation to reduce their stress, while patients who are expected to have shorter examinations can still be evaluated under air insufflation.

The use of a VAS or questionnaire for patients is common during stress assessments. Monitoring the salivary alpha-amylase (SAA) level was recently introduced as a convenient method to objectively assess psychological stress (12-14). Peripheral biomarkers reflecting autonomic activity had been lacking, and the emergence of SAA has provided a surrogate marker of sympathetic nervous system activity. SAA responds to both physical and psychological stressors, which correspond to the response patterns of the sympathetic nervous system. Whereas no correspondence between the plasma levels of norepinephrine and SAA could be established, associations between other markers of the autonomic nervous system, such as cardiovascular parameters, have been

found (15-18). Based on the pharmacological and electrophysiological literature, the pathways that lead to the secretion of SAA are clearly sympathetic/parasympathetic in nature (15-18). The findings of the association between SAA and the sympathetic nervous system indicate that SAA can function as a useful biomarker in acute and chronic stress studies (15-18). Indeed, SAA was used a as clinical biosensor for assessing surgery-related stress responses in a previous study (19). In the present study, the level of SAA immediately after colonoscopy or 30 minutes after colonoscopy did not show any significant differences between the carbon dioxide insufflation and air insufflation groups, likely because of the large standard deviation. The sum of the SAA at all three time points was significantly different. The establishments of standard or suitable comparison methods are future problems that need to be addressed when using SAA in clinical studies.

In conclusion, we demonstrated that carbon dioxide insufflation significantly reduced the post-examination discomfort as shown by both a VAS and salivary stress marker levels. Carbon dioxide insufflation shortened the post-examination discomfort time, abdominal fullness and pain and allowed a quicker recovery. The use of carbon dioxide rather than air insufflation reduced the patients' stress and may therefore contribute to better acceptance of colonoscopy. Carbon dioxide insufflation was especially useful to reduce the stress of patients who needed to undergo longer examinations.

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