

## Propofol-based sedation does not increase rate of perforation during colonoscopic procedure

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### Abstract

Sedation-related colonoscopic perforation (CP) has been under much debate. Our aim was to assess and compare the CP rate during colonoscopy by using sedation with or without propofol adjuvant. All patients who underwent colonoscopic procedure at the WGO Endoscopy Training Center, Siriraj Hospital, Thailand from March 2005 to October 2007 by using the intravenous sedation (IVS) technique were analyzed. The primary outcome was the CP rate; the secondary outcomes were sedation-related complications and death during and immediately after the procedure. There were 6140 colonoscopies and 1532 flexible sigmoidoscopies during the study period, of which 6122 colonoscopic procedures were performed by using IVS. All of these procedures were categorized into two groups: group A, the IVS technique was propofol-based sedation and group B, the IVS technique was non-propofol-based sedation. After matching the indications of procedure, there were 2022 colonoscopies in group A and 512 colonoscopies in group B. Colonoscopic procedures were performed by staff endoscopists (10.8%) or residents and fellows (89.2%). The characteristics of patients and sedative agents used in perforated patients in both groups were not significantly different. In group A, five patients (0.25%) suffered from perforation and two of them died. In group B, one patient (0.20%) had CP; the difference was not significant ( $P=0.829$ ). Our data showed that colonoscopy under propofol-based sedation did not increase the perforation rate. Serious complications are uncommon.

### Introduction

Colonoscopy is the most common diagnostic and therapeutic tool for colorectal carcinoma and is considered a routine procedure for patients with large bowel symptoms. Although

colonoscopy is regarded as a relatively safe procedure, it causes significant morbidity and rarely mortality. The most serious complication of colonoscopy is perforation.<sup>1,6</sup> The incidence of colonoscopic perforation (CP) could be as low as 0.02% in diagnostic colonoscopy and as high as 0.6% in therapeutic colonoscopy.<sup>7,8</sup> In addition, this procedure is uncomfortable and often causes sharp pain to patients. Controversy in safely using analgesics and sedatives during colonoscopy has always existed. The key concern is on perforation rate between colonoscopy with or without anesthesia.

Since 1974, colonoscopic procedures with sedation and/or anesthesia were thought by some people to be a risk factor for perforation.<sup>9</sup> However, a previous report by Kjaergard *et al.*<sup>12</sup> concluded that anesthesia administered by experienced staff is harmless and that general anesthesia for colonoscopy did not raise the risk of CP. Additionally, there is controversy regarding the frequency of sedation-related complications of colonoscopies especially for CP. Propofol-based sedation usually tends to deepen the sedation level and mask the earlier signs and symptoms of CP. The purpose of our study was to discover whether there is a difference in the incidence of CP between patients who received colonoscopy with or without propofol-based sedation.

### Materials and Methods

#### Patients

A total of 7672 consecutive patients from the WGO Endoscopy Training Center, Siriraj Hospital, Bangkok, Thailand were eligible for the study. These patients underwent colonoscopies (6140) and flexible sigmoidoscopies (1532) from March 2005 to October 2007. Inclusion criteria were age of  $\geq 18$  years and colonoscopic procedures performed using the intravenous sedation (IVS) technique. Exclusion criteria were patients younger than 18 years of age, procedures performed in the intensive care units, procedures performed without sedation, or procedures performed under monitored anesthesia care and general anesthesia.

#### Study design

This is a retrospective descriptive study. The primary outcome of the study was the CP rate during and immediately after the procedure. The secondary outcomes were sedation-related complications during and immediately after the procedure and mortality rate.

#### Assessment of colonoscopic perforation

After colonoscopy, all patients were observed

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in the recovery room for at least two hours before being discharged to the ward or home. We did not call each patient for a day after the procedure. However, the patients suspected of colonoscopic complications and those who underwent difficult procedures were admitted. In addition, all patients visited their endoscopists on the seventh day postendoscopy. The CP rate in both groups was recorded. Additionally, perforation site, type of endoscopist, and mortality rate in the two groups were assessed.

#### Sedation-related complications

All sedation-related complications were recorded. These complications were defined as: hypertension or hypotension (increase or decrease in blood pressure by 20% from baseline and above or below normal for age); tachycardia or bradycardia (increase or decrease in heart rate by 20% from baseline and above or below normal for age); any cardiac arrhythmias; hypoxia (oxygen desaturation,  $SpO_2 < 90\%$ ); airway obstruction.

#### Statistical analysis

Results were expressed as mean  $\pm$  SD or percentage (%), when appropriate. Comparisons between groups A and B were made by using  $\chi^2$ -tests (i.e. for categorical variables),  $\chi^2$ -tests for trend (for ordinal variables), and the two-sample independent t-test (for continuous variables). The statistical software package SPSS for Window Version 11 (SPSS Inc., Chicago, IL) was used to analyze the data. All statistical comparisons were made with the two-sided 5% level of significance.

## Results

There were 6140 colonoscopies and 1532 flexible sigmoidoscopies during the study period. Of these, 18 patients who underwent colonoscopy by using general anesthesia and monitored anesthesia care techniques were excluded. A total of 6122 colonoscopic procedures were performed by using IVS. All of these procedures were categorized into two groups. In group A, the IVS technique was propofol-based sedation. In group B, the IVS technique was non-propofol based sedation. We matched the indications of procedure between the two groups by the ratio of groups A and B (4:1). After matching, there were 2022 colonoscopies in group A and 512 colonoscopies in group B. Colonoscopic procedures were performed by staff endoscopists (10.8%) or residents and fellows (89.2%). Table 1 summarizes the clinical characteristics of the two groups. The mean ages in both groups were similar:  $57.7 \pm 15.7$  years in group A and  $58.3 \pm 14.5$  years in group B ( $P=0.573$ ). There were no significant differences between the two groups in age, sex, weight, ASA physical status, duration of procedure, or indication for colonoscopy.

For all patients, appropriate monitoring was used. Cardiorespiratory monitoring included continuous electrocardiogram, heart rate, oxygen saturation measurements, and five-minute interval noninvasive blood pressure measurements from a blood pressure cuff device. End-tidal carbon dioxide (CO<sub>2</sub>) monitoring with capnography was not used during sedation. The patients were given supplemental oxygenation via a face mask and sedated by well-trained anesthetic personnel directly supervised by a staff anesthesiologist in the endoscopy room. Anesthetic personnel included residents in anesthesiology and anesthetic nurses who were well trained in the use of the IVS technique and airway management. All sedated patients were sedated to either a moderate (conscious) or deep sedation level, according to guidelines of the American Society of Anesthesiologists<sup>14</sup> and the American Society of Gastrointestinal Endoscopy.<sup>15</sup>

Table 2 demonstrates the CP rate, perforation site, endoscopist, and mortality rate. Five patients (0.25%) on propofol-based sedation and one patient (0.20%) on non-propofol-based sedation had CP ( $P=0.829$ ). The sigmoid colon was the most common perforation site in both groups ( $P=0.624$ ). All of the perforations were performed by residents and fellows in both groups, except in one CP patient in the propofol-based group that was performed by a staff endoscopist. All perforations were recognized immediately during colonoscopy. Additionally, all CP patients underwent surgical management. Of these perforations, two deaths occurred in group A and none in group B

**Table 1. Characteristics of patients, duration of sedation, and indications of procedure (mean, SD, and percentage).**

	Group A (n=2022)	Group B (n=512)	P
Age (yr) (mean, SD)	57.7 (15.7)	58.3 (14.5)	0.573
Gender (%)			0.897
Male	812 (40.2)	204 (39.8)	
Female	1210 (59.8)	308 (60.2)	
Weight (kg) (mean, SD)	57.2 (12.5)	56.5 (11.4)	
ASA physical status (%)			0.984
I	528 (26.1)	132 (25.8)	
II	1120 (55.4)	284 (55.5)	
III	374 (18.5)	96 (18.7)	
Duration of procedure (min) (mean, SD)	30.8 (13.9)	30.6 (11.1)	0.591
Indication			0.481
Colorectal cancer	611 (30.2)	153 (29.9)	
Lower gastrointestinal hemorrhage	372 (18.4)	97 (18.9)	
Anemia	172 (8.5)	40 (7.8)	
Abdominal pain	261 (12.9)	73 (14.3)	
Bowel habit change	137 (6.8)	34 (6.6)	
Surveillance	109 (5.4)	28 (5.5)	
Others	360 (17.8)	87 (17.0)	

Group A, propofol based; Group B, non-propofol based.

**Table 2. Colonic perforation rate, perforation site, endoscopist, and mortality rate (n, %).**

	Group A (n=2022)	Group B (n=512)	P
Perforation rate	5 (0.25)	1 (0.20)	0.829
Perforation site			0.624
Sigmoid colon	4 (80.0)	1 (100.0)	
Hepatic flexure colon	1 (20.0)	0	
Endoscopist			0.829
Resident and fellow	4 (80.0)	1 (100.0)	
Staff	1 (20.0)	0	
Mortality rate	2 (22.2)	0	0.477

Group A, propofol based; Group B, non-propofol based.

**Table 3. Characteristics of patients and sedative agents used in perforated patients.**

	Group A (5)	Group B (1)	P
Age (yr) (mean, SD; range)	58.6 (23.1), 36-88	83.0	0.306
Gender (%)			0.273
Male	3 (60.0)	0	
Female	2 (40.0)	1 (100.0)	
Weight (kg) (mean, SD)	52.6 (11.4), 34-60	40.0	0.112
ASA physical status (%)			0.549
I	1 (20.0)	0	
II	2 (40.0)	0	
III	2 (40.0)	1 (100.0)	
Duration of procedure (min) (mean, SD; range)	64.0 (20.4), 30-80	50.0	0.199
Sedative agents			
Propofol (% mg/kg) n; mean (SD)	5 (100.0), 5.12 (3.17)	0	
Midazolam (% mg/kg) n; mean (SD)	5 (100.0), 0.02 (0.00)	1 (100.0), 0.04	0.014*
Fentanyl (% mg/kg) n; mean (SD)	5 (100.0), 0.001 (0.000)	1 (100.0), 0.001	0.741

Group A, propofol based; Group B: non-propofol based. \* considered statistically significant.

( $P=0.447$ ). Table 3 shows the characteristics of patients and the sedative agents used in the perforated patients. Only one patient in the non-propofol-based group had CP. There were no significant differences between the two groups in age, gender, weight, ASA physical status, and duration of procedure. Sedative agents including midazolam and fentanyl were commonly used in both groups. Mean dose of midazolam in group B was significantly higher than in group A ( $P=0.014$ ). Overall adverse events occurred in 602 patients (29.8%) in group A and in 118 patients (23.0%) in group B ( $P<0.001$ ). Most of the complications were hemodynamic alterations including hypotension, 28.1% in group A and 18.2% in group B; hypertension, none in group A and 1.8% in group B; bradycardia, 0.9% in group A and 2.0% in group B; and arrhythmia, 0.3% in group A and 0.8% in group B. These alterations were transient and did not require any specific interventions. There were no other procedure-related complications (Table 4).

## Discussion

In our present study, the rate of CP with or without propofol-based sedation was relatively higher than in our previous report<sup>16</sup> and other published series<sup>1-6</sup> (0.25% and 0.20% vs. 0.03-0.09%). One possible explanation of this difference is that the number of colonoscopies has increased markedly over the last few years. The majority of colonoscopic procedures were performed by the residents and fellows. It is also plausible that there are an increasing number of patients receiving IVS during colonoscopy, which may affect the endoscopist's perception of alarming pain experienced by the patients. Additionally, this report considered only colonoscopic procedures. If flexible sigmoidoscopy and colonoscopy done with IVS and other anesthetic techniques were included, the CP rate in our center was 0.09%.<sup>16</sup> However, the previous series did not mention the frequently used anesthesia/sedation technique. In our present study, we selectively collected the patients who underwent colonoscopy, not flexible sigmoidoscopy, by using the IVS technique. The result of our study also demonstrated that sedation was correlated to the CP indirectly. Consequently, the results of other studies<sup>17-20</sup> also confirmed that patients could withstand the colonoscopic procedure without anesthesia/sedation, and the rate of CP was fairly low with this technique without anesthesia/sedation. Colonoscopy under IVS has become a popular technique. Nevertheless, most patients undergoing endoscopy preferred sedation to relieve pain and anxiety.<sup>21-23</sup> Sedation itself provides an anxiolytic and amnesia,<sup>24,25</sup> and reduces cardiovascular stress.<sup>26</sup> Pain induced by the colonoscopic procedure is multifactorial and

**Table 4. Sedation-related complications during and immediately after procedure (n, %).**

	Group A (n=2022)	Group B (n=512)	P
Overall	602 (29.8)	118 (23.0)	<0.001*
Cardiovascular-related	592 (29.3)	116 (22.7)	<0.001*
Hypotension	568 (28.1)	93 (18.2)	
Hypertension	0	9 (1.8)	
Bradycardia	18 (0.9)	10 (2.0)	
Arrhythmia	6 (0.3)	4 (0.8)	
Respiratory-related	10 (0.5)	2 (0.4)	0.760
Hypoxia (SpO <sub>2</sub> <90%)	10 (0.5)	2 (0.4)	

Group A, propofol based; Group B, non-propofol based. \*considered statistically significant.

it is not easy for endoscopists to help reduce the pain without using analgesics or sedation. However, sedation during total colonoscopy should not be a substitute for good technique. Herman<sup>27</sup> demonstrated that 82% of patients who underwent colonoscopy required no analgesia or sedation. When sedation was necessary, smaller doses of medication were required. Colonoscopy without sedation could be important and useful for teaching the technique in training programs. Consequently, it was safer, less expensive, and allowed easier availability of colonoscopy. The previous study also showed that IVS for colonoscopy administered by experienced staff was harmless, and that general anesthesia for this procedure did not involve an increased risk of CP.<sup>28</sup> Our results demonstrated that propofol-based sedation does not increase the rate of CP in comparison to non-propofol-based sedation ( $P=0.829$ ). In our hospital, the colonoscopic procedure was performed usually by using the IVS technique. The sedative drugs that we commonly used were propofol, midazolam, and fentanyl. Propofol is a sedative without having an analgesic effect. According to the characteristics of propofol, such as quick onset of action with short-effect duration make it a suitable sedative for gastrointestinal endoscopy.<sup>29-31</sup> Additionally, it exhibits an inhibitory effect on spontaneous contractile activity and concentration-dependent depression of Ach-induced contraction on human gastric and colonic smooth muscles, although the mechanism is unknown.<sup>32</sup> Midazolam provides hypnotic, sedative, anxiolytic, amnesic, anticonvulsant, and centrally produced muscle relaxant properties. Fentanyl has a short half-life, potent analgesic effect, and rapid onset of action. Opioid receptors were related to modulation of colonic function; for instance, the  $\delta$ 2-opioid receptor agonist was a potent inhibitor in human colonic circular muscle<sup>33</sup> and  $\kappa$ -opioid receptor agonists cause dose-dependent, attenuated pressor and visceromotor responses to colorectal distension.<sup>34</sup> All these drugs are associated with less spastic colon in the colonoscopy procedure.

With standard patient monitoring during colonoscopy, using non-invasive blood pressure, pulse oximeter, and electrocardiography, seda-

tion-related complications can be identified and treated promptly before they become serious. The sedation with or without propofol adjuvant was relatively safe and effective.<sup>35</sup> Most common sedation-related complications were mild, transient, and easily treated.

Although it continues to be questionable whether a colonoscopy performed by a trainee increases the risk of CP, we cannot assess such a potential factor since the trainee-to-staff endoscopist ratio for all procedures in our study was unknown. Anderson and colleges<sup>36</sup> reported that there was not a significantly increased risk of CP performed by trainee fellows. Many training centers<sup>37-39</sup> have recommended that a minimum of 50-100 colonoscopies should be carried out by a trainee to gain endoscopic competency. In our center, the fellows and residents had performed 5-10 colonoscopies prior to the study. Their experiences were minimal. These factors may affect the CP rate. In our study, perforation at the sigmoid colon accounted for more than 75% of all CP sites in both groups. This findings was consistent with that of other studies.<sup>40,41</sup> All perforated patients in the current series underwent surgical management like ours. The choice between conservative and surgical management depends on clinical factors.<sup>42</sup> The CP rate in our report was rather high, and the mortality rate of our patients was relatively higher than in other series because of our patients' coexisting diseases. Furthermore, respiratory complications frequently occur after major abdominal surgery, particularly in advanced-age patients. Pneumonia was the primary cause of death in our study. There are several limitations in this study. First, inaccurate and incomplete documentation of certain measures, as occurs with many chart reviews, also occurred in this study. Second, although we searched the perforated cases as thoroughly as we could, there still exist cases we might have lost. For instance, the patient might receive emergency surgery by other nearby hospitals. Third, our practice employed only basic monitoring that does not include the use of end-tidal CO<sub>2</sub> for ventilation monitoring. Thus, respiratory adverse events may be underestimated. Fourth, our study examined the components for intravenous sedation and did not report on endoscopic findings in

patients with advanced age. Fifth, minor complications were not included in this study, which might lead to ignorance of the sedation-related complications. Finally, our study, which was a retrospective collection of cases from our data base, looked at all colonoscopic procedures in a given short-time period. Further studies should include a well-designed prospective study with close follow-up of every case receiving the colonoscopic procedure.

In summary, we concluded that propofol-based sedation does not increase a rate of perforation during colonoscopy procedure. All sedations with or without propofol adjuvant are relatively safe and effective when carried out by trained anesthetic personnel with appropriate monitoring. Additionally, colonoscopy is safe when performed by physicians in training. Serious complications are uncommon.

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