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CLINICAL TRIAL REPORT

Clinical Efficacy Between Intravenous Paracetamol and Intravenous Fentanyl for Propofol Deep Sedation in Colonoscopy: A Randomized Controlled Trial

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Introduction: Sedation practices for colonoscopy indeed vary widely around the globe. Due to a lack of data on intravenous paracetamol, we aimed to investigate the clinical efficacy of intravenous paracetamol compared to intravenous fentanyl under propofol deep sedation for colonoscopy.

Methods: A total of 225 patients who underwent colonoscopy at Siriraj Hospital were randomly assigned to two groups. All patients underwent deep sedation with propofol and received intravenous (iv) paracetamol (group P, n = 113) or iv fentanyl (group F, n = 112). All patients received a premedication of 0.02–0.03 mg/kg of midazolam intravenously. Fifteen to thirty minutes before the procedure, patients in group P were administered 1000 mg of iv paracetamol, while those in group F received 0.001 mg/kg of iv fentanyl. All patients were oxygenated with 100% O_2 via a nasal cannula, and deep sedated with titrated intravenous propofol. The primary outcome measure was the success rate of colonoscopy. The colonoscope reaching the ileocecal valve was an important marker for a successful colonoscopy. Secondary outcome measures included endoscopist and patient satisfaction, patient tolerance, ease of the procedure, and sedation-related complications during and immediately after the procedure.

Results: All colonoscopies were successfully completed. There were no significant differences in patient characteristics, duration of the procedure, endoscopist and patient satisfaction, patient tolerance, or ease of the procedure between the two groups. However, group F experienced significantly higher rates of upper airway obstruction and oxygen desaturation during the procedure compared to group P. No serious complications were observed in either group.

Conclusion: Intravenous paracetamol with propofol deep sedation in adult patients is non-inferior to intravenous fentanyl for successful colonoscopy completion. Sedation-related complications were relatively lower in the propofol deep sedation with iv paracetamol group compared to the propofol deep sedation with iv fentanyl group.

Registration: This trial was registered with the Thai Clinical Trial Registry (TCTR 20190321002).

Keywords: colonoscopy, propofol, deep sedation, intravenous paracetamol, fentanyl

Introduction

Colonoscopy is the standard procedure for diagnosis and treatment of colorectal diseases.[1] There are numerous cases each year. Because of short operative time and less invasive nature, colonoscopy is usually performed as an ambulatory procedure. Generally, the physicians know that this procedure causes only mild to moderate pain. A previous study on the pain experienced during colonoscopy revealed that mild, moderate, and severe pain was reported in 48%, 22% and 14% of procedures, respectively. Overall, nearly 64% of patients experienced mild to moderate pain.[2]

Sedation is commonly utilized for this procedure to ensure the patients comfort and to facilitate the procedure.[3] Most endoscopic procedures usually use intravenous (iv) sedation.[4] The common anesthetic agents are propofol, benzodiazepine, and opioids.[5] Propofol is particularly popular due to its short half-life and context-sensitive half time, allowing for

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early awakening without dizziness. However, it does carry the risk of hypotension and bradycardia.[5] Another commonly used benzodiazepine is midazolam. It has the fast onset within 1–5 minutes for anxiolysis and is suitable for colonoscopy. Although it may cause hypotension, the baroreceptor reflex compensates with an increased heart rate, resulting in minimal impact on the cardiovascular system.[5] Fentanyl, an opioid derivative, is widely used for procedural analgesia. Its properties are strong potent, fast onset, short duration, and minimal effects on the cardiovascular system. It is recommended for moderate to severe pain.[5]

The study conducted by Ahmadi et al aimed to assess and compare the clinical efficacy of iv paracetamol with fentanyl for moderate sedation in 96 patients, aged 18 to 75 years old, who underwent elective colonoscopy. The study demonstrated that there were no significant differences in terms of patient tolerance and satisfaction (P = 0.817 and 0.460, respectively). Consequently, the result showed that the incidence of hypotension and apnea was higher in the fentanyl group. Based on these results, it was concluded iv paracetamol is a suitable option for analgesia during colonoscopy.[6] The other study included 100 patients aged 18 to 55 years old who underwent laparoscopic cholecystectomy. The aim was to compare the efficacy of 1 mg iv paracetamol and 30 mg of ketorolac in assessing postoperative pain. It was found that both groups required no significant rescue doses of fentanyl. However, the ketorolac group had a slightly lower visual analog scale (VAS) score compared to the paracetamol group, although this difference there was not statistically significant.[7]

Another study conducted by Jelacic and coworkers involved 68 patients aged between 18 and 75 years old who were candidates for sternotomy. The efficacy of 1 gm iv paracetamol was compared with a placebo both before and during the operation. The findings indicated a significant reduction in the need for opioids in the paracetamol group, and the participants reported a high level of satisfaction.[8] Based on the statement mentioned, we are interested in exploring the use of non-opioid agents such as paracetamol. Our hypothesis is that iv paracetamol could be a valuable and effective analgesic agent for colonoscopic procedures. We also expect that iv paracetamol combined with midazolam and propofol infusion will yield similar results to using fentanyl in combination with midazolam and propofol infusion for colonoscopy.

Methods

After receiving approval from the Siriraj Institutional Review Board (SIRB) in January 2019 (Si 637/2018) and registering with the Thai Clinical Trial Registry (TCTR 20190321002). This study complied with the Declaration of Helsinki. A double blinded randomized controlled trial was conduct at Siriraj GI Endoscopy Center from March 2019 to November 2019. The study included the patients who were American Society of Anesthesiologists (ASA) class I–III, age over 18 years old, and who underwent colonoscopic procedures. The exclusion criteria included morbidly obese patients, patients with cardiorespiratory instability, severe liver or renal impairment, allergies to the studied drugs, a history of drug abuse, pregnancy, emergency cases, communication problems, and patient refusal. Patients who met the criteria were invited, and counseled during their appointment. At this time, they also received an information sheet about the study. The consent forms were completed on the day of procedure.

All patients were randomly assigned to one of two groups using computer-generated random numbers with blocks of eight. The first anesthetic staff member opened the sealed envelope containing the assigned group number. The study drug, prepared according to the protocol was then administered to the patient in the waiting room (Figure 1). Fifteen to thirty minutes before being transferred to the endoscopic room, the patients in group P were slowly infused with intravenous paracetamol 1000 mg which was covered by brown plastic bag, over a period of in 15 minutes. Then they received intravenous normal saline 1.5 mL immediately before moving to the colonoscopy. On the other hand, patients in group F were infused with iv normal saline, also covered by a brown plastic bag, over a period of 15 minutes. Before they moved into the endoscopic room, fentanyl 1 mcg/kg was given intravenously. The bottles and syringes containing the study drugs in both groups were removed before leaving the waiting room.

In the endoscopic room, the other anesthetic staffs who were not involved in the study drug administration provided care and administered anesthesia. All patients were given iv midazolam at a dose of 0.02 mg/kg. Induction was then performed slowly with a bolus of propofol at a rate of 0.5–1 mg/kg, followed by maintenance with a continuous infusion of propofol starting at 5 mg/kg/hr. The propofol infusion rate was adjusted and titrated to maintain a deep

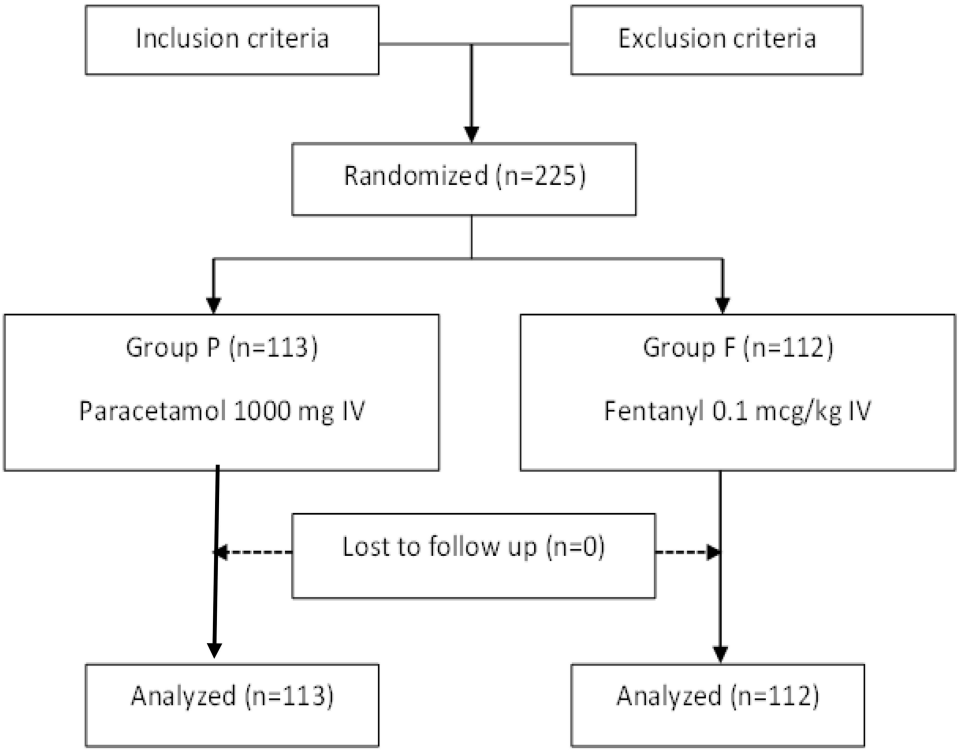

Figure 1 Consort flow chart.

sedation level, which was evaluated using the Observer's Assessment of Alertness/Sedation Scale (OAAS) with a score of 0 to 1. In the event of adverse events, such as hypotension the anesthetic staff managed and resolved the situation by administering crystalloid and vasopressor (ephedrine, norepinephrine). If there was upper airway obstruction, the airway was repositioned or adjunct airway equipment was used to open the airway. The anesthetic documents included the incidence of hypotension (systolic blood pressure <20% of baseline), desaturation (oxygen saturation < 90%), and apnea (breathing cessation > 20 sec), which were recorded. After the procedure, the patients were transferred to the post anesthetic recovery unit. Finally, the anesthetic staff who provided anesthesia, the endoscopists, and the patients completed the questionnaires to evaluate their experience.

The primary outcome of this study was to compare the successful completion rate between iv paracetamol and iv fentanyl during propofol deep sedation for colonoscopy. The successful completion is defined as the completion of colonoscopy as intended, without the need for additional drugs. The colonoscope reaching the ileocecal valve was an important marker for a successful colonoscopy. The secondary outcomes included evaluations of subjective satisfaction from endoscopists and patients as well as the ease of endoscopy. The endoscopist and patient satisfaction with sedation for the procedure was ranked as follows: 1 = very satisfied; 2 = satisfied; 3 = neutral; and 4 = dissatisfied. The ease of intubation of the endoscope was rated as follows: 1 = effortless; 2 = easy; 3 = fair; and 4 = difficult. In addition, sedation-related complications during and immediately after the procedure, were also noted. This study was designed as a randomized, double-blind, non-inferiority trial to determine whether propofol deep sedation with iv paracetamol is non-inferior to iv fentanyl for successful colonoscopy completion.

Statistical Analysis

A sample size of 112 patients per group provided 90% power ($1-\beta = 0.9$) to demonstrate non-inferiority of iv paracetamol to iv fentanyl, assuming a successful completion rate of 90% in both groups, a non-inferiority margin (δ) of 10% (meaning a completion rate difference of less than 10% would be considered clinically acceptable), a one-sided alpha (α) of 0.05, and allowing for a 10% dropout rate. The normality of continuous variables was assessed using the

Kolmogorov–Smirnov test and visual inspection of histograms. Normally distributed continuous data are presented as mean ± standard deviation (SD). Non-normally distributed continuous data are presented as median [interquartile range (IQR)]. Categorical data are presented as frequencies (n) and percentages (%).

The primary outcome, successful completion rate, was analyzed using a one-sided test for non-inferiority using the Wald Method. The non-inferiority of paracetamol to fentanyl would be concluded if the lower bound of the 95% confidence interval (CI) for the difference in completion rates (paracetamol minus fentanyl) is greater than -δ (−10%). Secondary outcomes, including patient tolerance, endoscopist satisfaction, ease of endoscopy, patient satisfaction, and the incidence of sedation-related complications, were compared between groups. For continuous secondary outcomes, the independent samples *t*-test (for normally distributed data) or the Mann–Whitney *U*-test (for non-normally distributed data) was used. Categorical secondary outcomes were analyzed using the chi-square test or Fisher's exact test, as appropriate. All statistical analyses were performed using SPSS for Windows, Version 17 (SPSS Inc., Chicago, IL, USA). A P value < 0.05 was considered statistically significant.

Results

The mean age of participants in both groups was 56.3 ± 10.4 years in group P and 56.5 ± 10.6 years in group F (P = 0.317). Most of the patients were classified as ASA class II. The body mass index was 23.8 ± 2.8 kg/m^2 in group P compared to 23.9 ± 2.8 kg/m^2 in group F (P = 0.327). The duration of the procedure was 29.5 ± 13.6 minutes in group P and 29.3 ± 13.8 minutes in group F. Therefore, there were no significant differences in the patients' characteristics and duration of the procedure (Table 1).

All colonoscopic procedures were completely successful in both groups (Table 2). There were no significant differences in the results of endoscopist satisfaction, patient satisfaction and ease of endoscopy. However, in terms of patient tolerance, group F was significantly better than group P (P = 0.021) (Table 3). Regarding sedation-related complications, there was no significant difference in these two groups (group P 8.8% vs group F 17.0%, P = 0.069). However, upper airway obstruction and oxygen desaturation during the procedure were significantly more common in group F than in group P. There were no serious complications in either group (Table 4).

Discussion

Colonoscopies are common procedures for prevention, diagnosis and treatment of colorectal diseases. Patients who performed these procedures feel mild to moderate pain or discomfort.[2] Although the conscious sedation that provided by endoscopists help to succeed the operation, previous studies show that anesthesiologists who dealt with deep sedation and experienced in airway management facilitated patient cooperation, endoscopic procedures, patient and endoscopist satisfaction.[9–11]

Table 1 Patient Characteristics and Baselines Parameters

	Group P (n=113)	Group F (n=112)	*P* value
Age (yr) (SD)	56.3 (10.4)	56.5 (10.6)	0.317
Sex (M/F) (n)	44/69	48/64	0.050
ASA physical status (I/II/III) (n)	32/77/4	41/66/5	0.357
Weight (kg) (SD)	62.8 (9.9)	62.6 (9.2)	0.338
Height (cm) (SD)	162.1 (7.5)	161.8 (7.6)	0.956
Body mass index (kg/m^2) (SD)	23.8 (2.8)	23.9 (2.8)	0.327
Duration of procedure (min) (SD)	29.5 (13.6)	29.3 (13.8)	0.574

Notes: Group P intravenous paracetamol; group F: intravenous fentanyl.
Abbreviations: ASA, American Society of Anesthesiologist; SD, standard deviation.

Table 2 Successful Completion Rate

	Group P (n=113)	Group F (n=112)	Difference	Difference (P-F) (95% confidence interval)		*P* value
				Lower	Upper	
Successful completion rate n (%)						>0.999
Yes	113 (100.0)	112 (100.0)	0.000	−0.0097	0.0097	
No	0	0				

Notes: Group P: intravenous paracetamol; group F: intravenous fentanyl. The value 0.001 was added to each zero when we performed the calculation, because zero cells can cause mathematical issues or inflate the Type I error rate in this case.

Table 3 Patient Tolerance, Endoscopist Satisfaction, Ease of Endoscopy and Patient Satisfaction

	Group P (n=113)	Group F (n=112)	*P* value
Patient tolerance n (%)			0.021*
Excellent	12 (11.5)	29 (25.9)	
Well	93 (82.3)	78 (69.6)	
Fair	7 (6.2)	5 (4.5)	
Poor	0	0	
Endoscopist satisfaction n (%)			0.056
Very satisfied	55 (48.7)	61 (54.5)	
Satisfied	50 (44.2)	50 (44.6)	
Neutral	8 (7.1)	1 (0.9)	
Unsatisfied	0	0	
Ease of endoscopy n (%)			0.123
Effortless	42 (37.2)	44 (39.3)	
Easy	53 (46.9)	61 (54.4)	
Fair	17 (15.0)	7 (6.3)	
Difficult	1 (0.9)	0	
Patient satisfaction n (%)			0.304
Very satisfied	100 (88.5)	94 (83.9)	
Satisfied	12 (10.6)	18 (16.1)	
Neutral	1 (0.9)	0	
Unsatisfied	0	0	

Notes: Group P: intravenous paracetamol; group F: intravenous fentanyl. *Considered to be statistically significant.

Table 4 Sedation-Related Complications

	Group P (n=113)	Group F (n=112)	*P* value
Hypotension n (%)	10 (8.8)	19 (17.0)	0.069
Upper airway obstruction n (%)	3 (2.7)	16 (14.3)	0.002*
Oxygen desaturation, n (%)	0	4 (3.6)	0.043*

Notes: Group P: intravenous paracetamol; group F: intravenous fentanyl. *Considered to be statistically significant.

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Paracetamol, also known as acetaminophen, is not typically used alone as an analgesic agent for endoscopic procedures. Instead, it is commonly administered as an adjunct to long side other sedatives, such as propofol or benzodiazepines, to provide additional pain relief and enhance patient comfort during the procedure.[12] Fentanyl is a potent synthetic opioid with no intrinsic anxiolytic or amnestic properties. It has a rapid onset, short duration of action, lack of direct of myocardial depressant effects, making it ideal drug for use endoscopic sedation. Intravenous fentanyl can be easily and rapidly titrated for painful procedures. While paracetamol itself does not have sedative properties, its analgesic effects can help reduce pain and discomfort experienced by patients undergoing endoscopy. By minimizing procedural pain, paracetamol indirectly contributes to a more relaxed and comfortable state for patients, potentially making the sedation process easier.

The efficacy of iv paracetamol in this context lies mainly in its ability to supplement other sedative medications, rather than acting as a sedative agent itself. It can help lower the overall dosage requirements of sedatives or opioids. Several studies that have examined the use of iv paracetamol as part of multimodal analgesia protocol for endoscopic procedures have shown promising results in terms of improved pain management, patient satisfaction, and reduced opioid consumption. Overall, iv paracetamol can play a valuable role in optimizing sedation and analgesia protocol for endoscopic procedures by enhancing pain management and potentially decreasing the need for higher doses of sedative medications.[13] However, one limitation of using paracetamol in colonoscopy is the time required for paracetamol to reach its maximum analgesic effect, which can lead to delays in performing the colonoscopy.

Paracetamol and fentanyl could be used as adjuncts to propofol for sedation during colonoscopy, but they work through different mechanisms and may have different profiles of efficacy and safety. Eventually, the selection of paracetamol or fentanyl as adjuncts to propofol for deep sedation during colonoscopy should be based on a careful assessment of the patient's needs, risk factors, and the procedural context, with consideration given to efficacy, safety, and patient comfort. Additionally, the choice of analgesic adjunct can impact various aspects of the colonoscopic procedure, including its duration, patient tolerance, and successful completion rate. Both fentanyl and paracetamol can contribute to achieving optimal conditions for colonoscopy. In our study, endoscopist and patient satisfaction as well as the ease of endoscopy, were rated as very satisfied and easy in both groups. Although patient tolerance was significantly greater in the fentanyl group compared to the paracetamol group, sedation-related complications were significantly higher in the fentanyl group.

A meta-analysis was published demonstrating that a single dose of iv paracetamol provides 50% pain relief over a period of 6 hours and reduces opioid requirements by 30% over 4 hours.[14] The use of paracetamol instead of tramadol (a weak opioid) for medical sedation has been found to decrease the adverse events, such as over-sedation and respiratory depression.[15] There was limited data on the use of deep sedation using iv paracetamol for colonoscopy. Our results indicated that both groups had successful colonoscopies. We believe that iv paracetamol 1000 mg provided sufficient pain relief during the colonoscopic procedure. A previous study comparing midazolam combined with iv paracetamol to midazolam plus fentanyl also reported successful completion of all procedures.[6] In addition to success rate, it is important to evaluate the patient and endoscopist satisfaction. Similar to previous studies, our study found no significant differences in satisfaction levels.

Paracetamol used in propofol deep sedation for colonoscopy, may result in fewer sedation-related complications compared to fentanyl. It is generally considered safer than opioids like fentanyl in terms of respiratory depression and other opioid-related adverse effects. Fentanyl is known to significantly depress respiratory drive more than paracetamol and can commonly cause hypotension and bradycardia, especially when administered in larger doses or rapidly. In the study conducted by Ahmadi et al, it was detected that the incidence of upper airway obstruction and hypoxia was significantly lower in the paracetamol group compared to the fentanyl group. This study indicated that fentanyl led to a higher incidence of respiratory depression compared to the paracetamol group, even when used alongside midazolam for conscious sedation. The authors suggested that the respiratory-related adverse events were due to the synergistic effect of fentanyl with propofol deep sedation.[6] Although our study did not directly assess the procedure-related complications, we did not observe any serious complications during or after the procedures. Our previous study also confirmed that colonoscopy under propofol-based sedation did not increase the perforation rate, and serious complications were uncommon.[16]

Fentanyl may require more time to fully regain consciousness and normal respiratory function. Both fentanyl and paracetamol can provide pain relief when used with propofol. In procedures such as colonoscopy, adequate pain control is essential for patient comfort and procedural success. However, excessive opioid analgesia may increase the risk of sedation-related complications, especially respiratory depression. Overall, our study demonstrated that sedation-related complications are lower with iv paracetamol compared to iv fentanyl in propofol deep sedation for colonoscopy. It may indicate that paracetamol is a safer alternative in this context, particularly for patients at higher risk of sedation-related adverse events. Nevertheless, further studies, including randomized controlled trials, are necessary to confirm these findings and establish the optimal sedation regimen for colonoscopy.

Because of its safety and fewer complications, iv paracetamol is considered an appropriate alternative for analgesia during colonoscopy. The authors suppose that paracetamol which lacking of respiratory depression, will be superior for the vulnerable patients especially the elderly, obese, and those with obstructive sleep apnea. Additional studies are needed to find out the cost-effectiveness and potential complications in these specific patient populations. These outcomes hold significant value for ambulatory surgery. The strength of this study lies in its design as a randomized controlled trial conducted at a single center, ensuring that procedures and anesthetic techniques were consistent across the entire population. Consequently, there are few studies that focus on the benefits of iv paracetamol for ambulatory colonoscopy cases, making this study predominantly valuable.

There are several limitations in our study. First, the variety of experience levels among staff and trainees in the endoscopic and anesthetic teams may have impacted study conduction and data gathering, potentially biasing the results, including the successful completion rate and ease of intubation. However, this effect may be small given the high successful completion rate of the procedures and the equal amount of time used for the completion of the procedures in both groups. Second, we did not use the capnometry during the procedure. Capnometry provides objective and continuous monitoring of ventilation, allowing healthcare providers to detect and respond to subtle respiratory changes early. Its absence during sedation can lead to missed detection of transient or mild adverse events, which might not be reported. Third, our study did not evaluate pre-procedure anxiety, which could have influenced the outcome of the study. Fourth, the study included ease of intubation and satisfaction scales that had not been previously validated. As these reported scales are secondary outcomes, the result of the primary objective remained unbiased by the use of these scales. Despite the limitations discussed, we are confident that our findings could be generalized to the practice of colonoscopy, suggesting that iv paracetamol could be a feasible alternative to fentanyl for high-risk patients undergoing propofol deep sedation.

Conclusion

Propofol deep sedation combined with iv paracetamol was safe and effective to complete the colonoscopy. On contrary, the sedation-related complications including upper airway obstruction and hypoxia were significantly higher in the fentanyl group. Intravenous paracetamol was the alternative analgesic adjuvant for colonoscopy. However, further studies focusing on high-risk populations would be necessary to solidify iv paracetamol's role in sedation practices.

Abbreviations

ASA, American Society of Anesthesiologists ASA; OAAS, Observer's Assessment of Alertness/Sedation Scale; SD, standard deviation; CI, confidence interval; IQR, interquartile range; NRS, numeric rating score; PCEA, patient-controlled epidural analgesia; PIEB, programmed intermittent epidural bolus.

Data Sharing Statement

The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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