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ORIGINAL RESEARCH

Effect of Oliceridine on Sufentanil-Induced Cough During General Anesthesia: A Prospective Randomized Controlled Clinical Study

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Background: Sufentanil-induced cough (SIC) frequently occurs during the induction of general anesthesia and may result in serious clinical complications, occasionally posing life-threatening risks. In clinical practice, we observed that oliceridine—a G protein-biased μ-opioid receptor agonist—demonstrates a potent suppressive effect on SIC. This study aimed to evaluate the efficacy of oliceridine in preventing SIC and to assess any associated adverse events.

Methods: In this prospective, randomized, double-blind, placebo-controlled trial, 286 adult patients undergoing elective surgery under general anesthesia were enrolled and randomly assigned to receive either 2 mg oliceridine (OS group) or an equal volume of normal saline (SS group) before intravenous administration of sufentanil. The primary outcome was the incidence of SIC. Secondary outcomes included the severity of cough, vital sign changes, and adverse events.

Results: The incidence of SIC was 42.66% in the SS group and 0% in the OS group (95% upper confidence bound ≈ 2.6%; $P < 0.001$). Among the SS group, mild, moderate, and severe cough occurred in 12.59%, 26.57%, and 3.50% of patients, respectively. No significant differences were observed in systolic or diastolic blood pressure, heart rate, or SpO_2 between the two groups at baseline or 2 minutes post-sufentanil administration. The incidence of adverse events was low and comparable between groups, with no reported cases of apnea, nausea, or vomiting.

Conclusion: Pretreatment with 2 mg oliceridine demonstrated favorable effevtiveness in suppressing SIC without significant adverse effects. Oliceridine appears to be a safe and effective prophylactic strategy for preventing SIC and may have valuable clinical utility in anesthesia practice.

Keywords: oliceridine, sufentanil, opioid-induced cough, general anesthesia, μ-opioid receptor

Introduction

Sufentanil, a potent synthetic opioid analgesic, is widely used in clinical anesthesia for its rapid onset and strong analgesic properties. However, intravenous administration during anesthetic induction may provoke a reflex cough, with a reported incidence of up to approximately 35%.[1] Clinically, sufentanil-induced cough (SIC) has been associated with abrupt increases in blood pressure, as well as elevated intraocular, intracranial, intrapulmonary, and intra-abdominal pressures, and may even result in upper airway obstruction. In certain cases, the cough reflex can be spasmodic and

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explosive, and may occasionally become life-threatening.[2,3] These adverse events pose significant risks to patient safety and perioperative outcomes.

Various pharmacological interventions, including lidocaine, atropine, magnesium sulfate, dexamethasone, propofol, midazolam, muscle relaxants (rocuronium, vecuronium), ketamine, pentazocine, tramadol, α_2-agonists (clonidine, dexmedetomidine), β_2-agonists (terbutaline, ephedrine), sodium cromoglycate, beclomethasone, salbutamol, and dextromethorphan, as well as non-pharmacological methods such as opioid pretreatment, dilution, and slow injection, have been employed to manage opioid-induced coughing (OIC).[4] Unfortunately, the efficacy and safety of these antitussive interventions remain controversial.[4]

Oliceridine is a biased μ-opioid receptor agonist approved by the US Food and Drug Administration (FDA) in 2020, primarily as an alternative therapy for acute pain in adults inadequately managed with traditional opioids.[5] Clinically, we observed that oliceridine significantly suppresses SIC during induction, yet this has been rarely reported previously. To address this clinical issue, we designed a prospective, randomized, double-blind, placebo-controlled study to clarify the effects of oliceridine on SIC during anesthesia induction.

Materials and Methods

Study Design and Ethics

This study was a prospective, single-center, randomized, double-blind, placebo-controlled, clinical trial. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Ethics Committee of the First People's Hospital of Tianshui (Approval No.: 2025–06; Date of approval: April 2, 2025). The trial was registered in the Chinese Clinical Trial Registry (Registration No.: ChiCTR2500100414). This report adheres to the Consolidated Standards of Reporting Trials (CONSORT) guidelines. Written informed consent was obtained from all participants and their legal guardians prior to study enrollment.

Enrollment

Patients were initially recruited through informational brochures distributed in the surgical wards of the First People's Hospital of Tianshui. Inclusion criteria were as follows: age between 18 and 70 years, American Society of Anesthesiologists (ASA) physical status I–III, and scheduled to undergo elective surgery under general anesthesia. Patients were excluded based on the following criteria: history of drug allergy; sinus bradycardia; severe neurological, respiratory, or cardiovascular disorders; anesthetic drug dependence or recent opioid use; smoking history; hepatic or renal dysfunction; pregnancy, lactation, or delivery-related surgeries; and upper respiratory tract infection within two weeks prior to surgery, which could predispose patients to spontaneous coughing.

Randomization and Blinding

Patients were randomly assigned to either the Oliceridine group (OS) or Saline group (SS) in a 1:1 ratio using simple randomization via random sequence generator (http://www.random.org). The allocation results were concealed in sealed opaque sequentially numbered envelopes that were provided to the research coordinator. On the day of surgery, the research coordinator delivered the envelope to an unblinded drug preparer, who was not involved in subsequent study procedures. According to the assigned protocol indicated within the envelope, the drug preparer prepared the study medications. In the OS group, oliceridine (2 mg) was diluted with normal saline to a final volume of 5 mL; in the SS group, 5 mL normal saline alone was used. The two study drugs were placed into identical syringes, which were subsequently labeled as "Syringe 1" and "Syringe 2". After preparation, the drug preparer delivered the syringes containing the study drugs to the investigator responsible for drug administration. They resealed the envelopes and then returned them to the research coordinator. The study medications were maintained at room temperature (20°C–22°C) and administered within 10 minutes of preparation. Patients, the research coordinator, the investigator responsible for drug administration, and the statistician were all blinded to the group allocation and drug identity throughout the study.

Anesthesia and Procedure

An intravenous (IV) cannula (22G) was inserted into the dorsum of the right forearm for each patient, followed by continuous infusion of balanced crystalloid solution. Standard monitoring, including heart rate, noninvasive blood pressure, and peripheral oxygen saturation, was initiated upon arrival in the operating room and maintained until the completion of surgery.

Sufentanil was diluted with normal saline to achieve a final concentration of 5 μg/mL, and the syringe was clearly labeled with the drug name and concentration. All patients received an intravenous injection of either 2 mg oliceridine (OS group) or an equal volume of 0.9% normal saline (SS group), administered over 3–5 seconds prior to anesthetic induction. The selected 2 mg intravenous dose was determined with reference to the dosing standards approved by the US Food and Drug Administration for oliceridine in the management of acute pain, and considering an appropriate balance between efficacy and safety. This was immediately followed by an intravenous bolus of prepared sufentanil 0.5 μg/kg, administered over 2 seconds. The occurrence and severity of reflex cough were assessed in real time by a blinded observer positioned at the patient's bedside within 2 minutes following sufentanil administration. The present study determined the observation period for SIC to be within 2 minutes, in accordance with methodological designs reported in previous studies[6–8] on OIC and supported by clinical practice experience. No other medications were given to the patients prior to the administration of the study drugs.

Upon completion of the observation period or in the event that oxygen saturation dropped below 90%, anesthesia induction was initiated with propofol (1–1.5 mg/kg) and rocuronium (0.9 mg/kg), followed by positive pressure ventilation.

Outcome Measurement

All outcomes were assessed and documented by the research coordinator. The primary outcome of this study was the incidence of cough following intravenous administration of sufentanil. Secondary outcomes included: (1) The number of patients experiencing varying degrees of cough severity (mild [1–2 coughs], moderate [3–5 coughs], and severe [>5 coughs]);[9] (2) Systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and peripheral oxygen saturation (SpO_2), recorded at baseline immediately prior to administration of oliceridine or normal saline (T0), and at 2 minutes after sufentanil injection (T1); (3) Other adverse events related to oliceridine and sufentanil, such as truncal rigidity, oxygen desaturation (defined as SpO_2 <90%), apnea, nausea and vomiting.

Sample Size Calculation

The sample size calculation was performed using PASS 15 software (NCSS, LLC, Kaysville, UT, USA) based on the primary outcome, which was the incidence of cough following intravenous administration of sufentanil. Referring to previous reports, the incidence of SIC during anesthetic induction was approximately 35%.[1] We hypothesized that pretreatment with oliceridine would reduce this incidence by 50%, to an expected incidence of 17.5%. The sample size was estimated using a two-sided Z-test for two independent proportions (unpooled variance). Therefore, at least 128 patients per group were required to achieve 90% statistical power at a two-tailed significance level (α) of 0.05. Considering a potential dropout rate of approximately 10%, a total of 143 patients per group were enrolled in this study.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics software (Version 22.0; IBM Corp., Armonk, NY, USA) in the intention-to-treat (ITT) population, which included all randomized patients. A two-tailed P-value < 0.05 was considered statistically significant. Secondary outcomes were designated as exploratory, without adjustment for multiplicity.

Categorical variables were expressed as numbers (percentages) and compared using Fisher's exact test owing to zero-cell issues. Effect sizes were reported as absolute risk reduction (ARR) and number needed to treat (NNT), with corresponding 95% confidence interval (CI). Relative risks (RR) were additionally calculated using the Haldane–Anscombe correction for zero-cell counts. Between-arm comparisons of ordinal categorical variables were not estimable due to zero-cell counts in the treatment group; therefore, only descriptive distributions were presented for the control group.

Continuous variables were presented as means ± standard deviation (mean ± SD). Given the large sample size, *t*-tests were considered acceptable, with distributional assumptions assessed using Q–Q plots and residual diagnostics. Repeated-measures mixed-effects models with fixed effects for group, time, and their interaction (group×time), and random intercepts for subjects, were used to analyze continuous outcomes. Results were presented as a single group×time P value with β estimates and 95% CI.

Outcomes

A total of 318 patients were initially screened for eligibility. Among them, 286 met all inclusion and exclusion criteria and were randomly assigned in a 1:1 ratio to the OS group or the SS group. Thirty-two patients were excluded due to not meeting eligibility criteria, declining participation, or changes in the planned anesthesia protocol. All randomized patients completed the study and were included in the final analysis, with no dropouts observed (Figure 1). Because of the randomization procedure, baseline demographic characteristics and sufentanil administered during induction were well balanced between the two groups (Table 1).

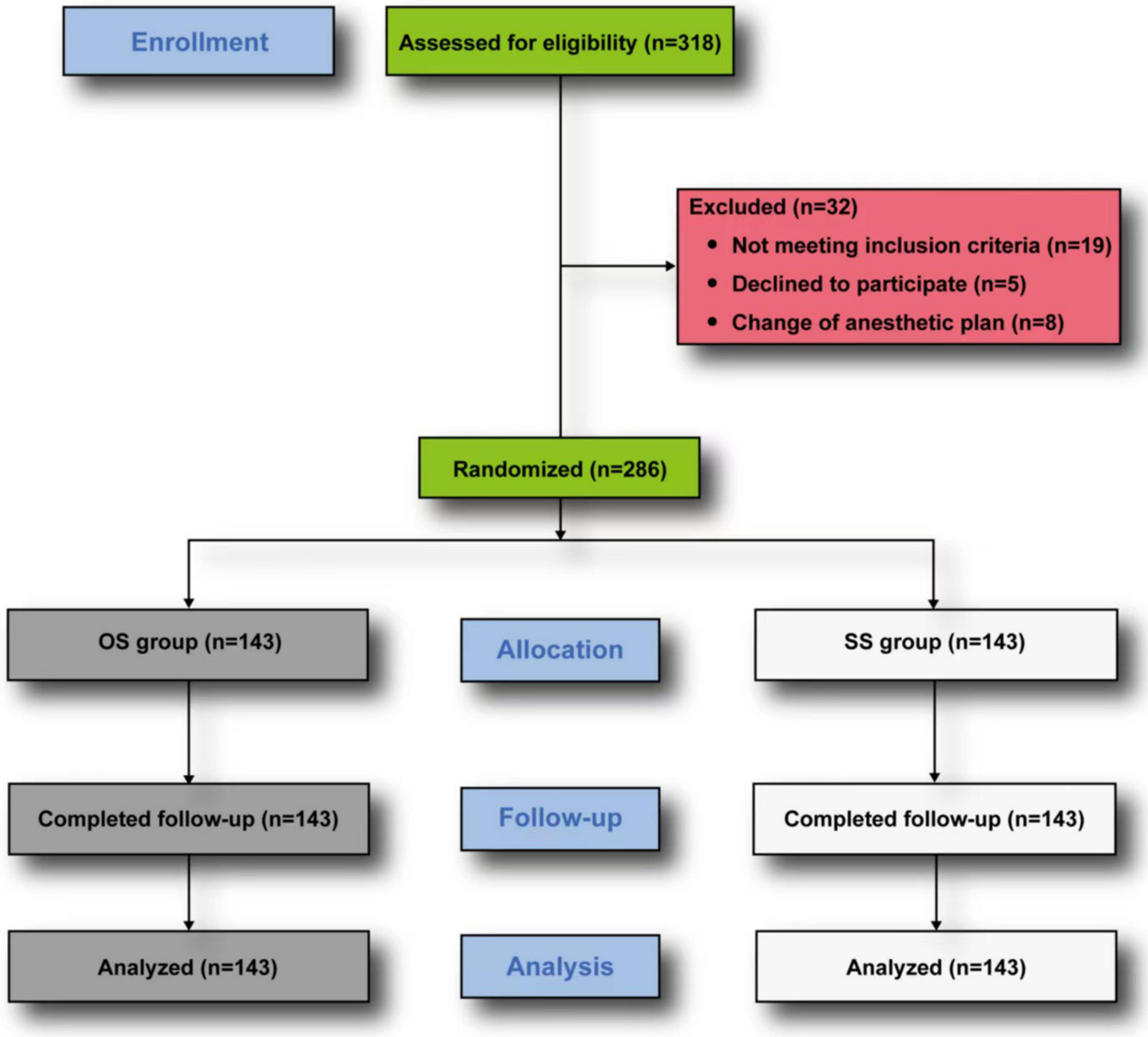

Figure 1 Consolidated standards of reporting trials flow diagram.
Abbreviations: OS group, Oliceridine group; SS group, Saline group.

Table 1 Demographic Characteristics and Total Dose of Sufentanil

Parameter	OS Group (n = 143)	SS Group (n = 143)
Age (years)	55.72±15.34	53.43±13.63
Gender, male/female	68/75	53/90
Weight (kg)	65.70±11.91	63.65±10.49
Height (cm)	163.30±8.51	163.47±7.75
ASA class (I/2/3)	12/122/9	13/122/8
Total dose of sufentanil (μg)	32.85±5.95	31.82±5.24

Note: Data were presented as mean ± SD, or number of patients.
Abbreviations: ASA, American Society of Anesthesiologists physical status; OS group, Oliceridine group; SS group, Saline group.

No patients in the OS group experienced SIC during anesthetic induction (95% upper confidence bound ≈ 2.6%), whereas the incidence in the SS group was 42.66%, with rates of mild, moderate, and severe coughing at 12.59%, 26.57%, and 3.50%, respectively. The difference in the incidence of SIC between the two groups was statistically significant ($P < 0.0001$; 42.66% vs 0%; Table 2). The difference in the incidence of severity of SIC between the two groups could not be compared because no coughing events occurred in the OS group.

Repeated-measures mixed-effects models showed no significant group×time interactions for SBP, DBP, HR, or SpO_2, indicating comparable peri-induction trajectories between the two groups. (Table 2). In the SS group, one patient developed transient limb rigidity without accompanying oxygen desaturation, and no intervention was required. In the OS group, one patient experienced a transient drop in oxygen saturation to 87%, which resolved promptly after jaw lift,

Table 2 Incidence and Severity of Sufentanil-Induced Cough, Vital Sign Changes, and Adverse Events After Treatment in Both Groups

Parameter	OS Group (n = 143)	SS Group (n = 143)	Estimate (95% CI)	P value
Incidence of cough, n (%)	0 (0)	61 (42.7)	ARR%: 42.7 (32.2, 50.9); NNT: 3 (2, 4); RR: 0.016 (0.002, 0.115)*	<0.0001[a]
Severity of cough, n (%)			Not estimable	NA
Mild	0 (0)	18 (12.6)		
Moderate	0 (0)	38 (26.6)		
Severe	0 (0)	5 (3.5)		
SBP, mmHg			β: 3.4 (−2.8, 9.7)	0.283[b]
T0	125.6±19.6	128.6±21.1		
T1	126.4±18.2	125.0±15.5		
DBP, mmHg			β: 2.3 (−1.8, 6.4)	0.279[b]
T0	75.5±13.9	77.7±15.3		
T1	73.4±11.1	72.7±10.8		
HR, beats/min			β: 1.1 (−2.6, 4.8)	0.561[b]
T0	69.0±11.0	70.4±12.0		
T1	67.3±10.7	68.1±11.5		
SPO_2, %			β: 0.1 (−0.4, 0.6)	0.759[b]
T0	97.4±1.6	97.6±1.5		
T1	96.4±1.6	96.5±1.4		
Adverse events, n (%)				
Truncal rigidity	0 (0)	1 (0.7)	ARR%: 0.7 (−0.7, 2.1)	1.000[a]
Hypoxemia	1 (0.7)	0 (0)	ARR%: −0.7 (−2.1, 0.7)	1.000[a]

Notes: Data were presented as mean ± SD; or as number (%). [a]Fisher's exact test; [b]mixed-effects model. *Haldane–Anscombe correction applied due to zero events in the oliceridine group.
Abbreviations: ARR, absolute risk reduction; NNT, number needed to treat; RR, relative risk; CI, confidence interval; NA, not applicable; β represents the estimated between-group difference in change (OS group – SS group) from mixed-effects models including fixed effects for group, time, and their interaction, with random intercepts for subjects; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; SpO_2, peripheral oxygen saturation; T0, immediately prior to administration of oliceridine or normal saline; T1, 2 minutes after sufentanil injection; OS group, Oliceridine group; SS group, Saline group.

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with SpO_2 returning above 90% (Table 2). However, the between-group differences in the incidence of muscle rigidity and oxygen desaturation were not statistically significant. No patients in either group experienced apnea or nausea and vomiting as adverse events.

Discussion

The results of this study demonstrated that the incidence of SIC reached as high as 42.7%, consistent with previously reported findings. Pretreatment with oliceridine was associated with no observed cases of SIC in this study (95% upper confidence bound ≈ 2.6%), while maintaining stable vital signs and without significant adverse effects. To our knowledge, this finding has not been previously reported.

Reflex coughing frequently occurs after opioid administration during anesthetic induction. The reported incidence of OIC varies widely across studies.[10–13] Numerous factors may influence the occurrence of OIC, including opioid dose and concentration, order of administration, speed and site of intravenous injection, individual physiological characteristics, age, sex, body weight, medical history, smoking status, and genetic predisposition.[14] However, the underlying mechanisms of opioid-induced cough remain poorly understood. One hypothesis suggests that opioids significantly suppress central sympathetic nervous system activity following injection, leading to a relative increase in vagal tone that may trigger coughing.[15] Another proposed mechanism involves the activation of pulmonary chemoreflex pathways mediated by vagal C-fiber receptors located near pulmonary vessels, resulting in bronchoconstriction and cough.[16] Reduced chest wall compliance following opioid administration may also lead to sudden vocal cord adduction or supraglottic obstruction, provoking a cough reflex.[17]

Furthermore, the release of substances like histamine and neuropeptides acting on presynaptic μ-opioid receptors has been implicated in cough induction.[3] In addition, a previous study suggested that opioid receptor dualism may also play a role in mediating cough. Opioids primarily produce antitussive effects through their actions on central opioid receptors, whereas preferential activation of peripheral receptors has been associated with cough induction.[9]

A randomized controlled trial conducted by Zhang J demonstrated that pretreatment with remifentanil significantly reduced the incidence of SIC. The authors attributed this effect to the preferential occupancy of μ-opioid receptors by remifentanil, thereby preventing sufentanil from eliciting its tussive effect through the same receptor pathway.[1] As a G protein-biased μ-opioid receptor agonist,[18] oliceridine may exert a similar receptor-occupying effect when used as a pretreatment, which could represent a primary mechanism by which it suppresses SIC. Additionally, a randomized controlled study by Chengyong Gu reported that low-dose fentanyl pretreatment attenuated cough responses induced by subsequent high-dose fentanyl administration. This effect was hypothesized to result from the depletion of neurotransmitters in peripheral nerve fibers, particularly in pulmonary vagal C-fiber terminals.[12] Accordingly, it is plausible that oliceridine pretreatment similarly depletes neurotransmitters from rapidly adapting receptors, constituting another potential mechanism for the suppression of SIC. Moreover, the concurrent use of two opioids may enhance central inhibitory effects, leading to simultaneous suppression of both sympathetic and vagal tones and thereby preventing autonomic imbalance. Central muscle relaxation induced by opioid co-administration may also help prevent vocal cord closure and preserve respiratory muscle tone, further contributing to the attenuation or elimination of SIC.

Currently, several agents have been identified as effective in reducing opioid-induced cough, including butorphanol, lidocaine, ketamine, dexmedetomidine, fentanyl, propofol, dezocine, dexamethasone, and magnesium sulfate.[19–21] However, most of these agents do not completely eliminate OIC and are associated with a variety of adverse events. High-dose lidocaine, when used during induction of general anesthesia, may cause arrhythmias and cardiovascular depression.[22] Ketamine has been reported to induce hallucinations and elevate blood pressure, intraocular pressure, and intracranial pressure.[20] Dexmedetomidine may result in hypotension and bradycardia,[23] while dexamethasone is associated with hyperglycemia and increased risk of infection. Magnesium sulfate has been linked to nausea, vomiting, and dyspnea.[24] Although dezocine and butorphanol have shown near-complete suppression of OIC, they are also associated with adverse events such as respiratory depression and postoperative nausea and vomiting.[8,14,19,25] Additionally, both propofol and fentanyl carry the risk of significant respiratory and cardiovascular depression.[20] In contrast, the results of the present study demonstrated that pretreatment with oliceridine effectively suppressed SIC without inducing any clinically significant adverse events. Compared to the aforementioned agents, oliceridine may offer superior clinical utility due to its favorable efficacy and safety profile.

This study has several limitations. First, it did not evaluate the efficacy of oliceridine pretreatment in suppressing cough induced by other opioid agents. Second, the optimal dose of oliceridine for the prevention of SIC was not explored. Additionally, potential long-term adverse effects associated with the combined use of these two opioids were not assessed. In future studies, we aim to further investigate the efficacy and safety profile of oliceridine in preventing OIC.

Conclusion

In conclusion, pretreatment with 2 mg of oliceridine demonstrated favorable effectiveness in reducing both the incidence and severity of SIC without producing any significant adverse effects. These findings suggest that oliceridine may be a promising adjunct for use during the induction of general anesthesia. As a preventive strategy against SIC, oliceridine demonstrates clinical potential and merits further investigation and broader application.

Data Sharing Statement

The data are available from the corresponding author (fankunmazui@hotmail.com) on reasonable request.

Ethical Statement

This study strictly abided by the CONSORT reporting criteria for RCT. The study was ethically endorsed by the First People's Hospital of Tianshui (Approval No.: 2025-06; Date of approval: April 2, 2025) and registered at the Chinese Clinical Trial Registry (Registration No.: ChiCTR2500100414).

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.

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Disclosure

The authors report no conflicts of interest in this work.

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