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STUDY PROTOCOL

Effect of Intrathecal Hydromorphone on the Duration and Efficacy of Postoperative Analgesia in Patients Undergoing Benign Anorectal Surgery: Protocol for a Randomized, Double-Blind, Controlled Trial

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Background: Intrathecal anesthesia is commonly used for analgesia in anorectal surgery, often supplemented with low-dose opioids such as morphine or fentanyl to prolong the duration of analgesia. However, the utility of these opioids is constrained by their adverse effects or inadequate analgesia. Hydromorphone, an opioid with pharmacodynamic properties intermediate between those of morphine and fentanyl, theoretically offers a favourable balance of prolonged analgesia and reduced side effects. Nevertheless, evidence regarding the efficacy and safety of intrathecal hydromorphone for postoperative analgesia in anorectal surgery remains scarce.

Purpose: To determine whether the addition of hydromorphone can effectively prolong the duration of analgesia provided by single-agent intrathecal ropivacaine, reduce the requirement for rescue analgesics, and avoid a significant increase in adverse effects.

Patients and Methods: A total of 76 patients scheduled for elective benign anorectal surgery will be enrolled and randomly allocated in a 1:1 ratio to either the intervention group (Group H: intrathecal ropivacaine 10 mg + hydromorphone 75 μg) or the control group (Group C: intrathecal ropivacaine 10 mg). The primary outcome will be the duration of postoperative analgesia, defined as the time to first request for rescue analgesia. Secondary outcomes will include Numerical Rating Scale (NRS) pain scores at various postoperative time points (4, 6, 8, 10, 12, and 24 hours), total 24-hour rescue analgesic consumption, the incidence of adverse effects, and patient satisfaction.

Conclusion: To our knowledge, this is one of the first randomized controlled trials to evaluate the analgesic value of intrathecal hydromorphone in patients undergoing anorectal surgery. If the outcomes are positive, this approach may offer a superior multimodal analgesic option for anorectal procedures, support the implementation of Enhanced Recovery After Surgery (ERAS) protocols, and provide high-quality evidence to inform clinical decision-making in this field.

Trial Registration: The study was registered with the Chinese Clinical Trial Registry (Registration No.: ChiCTR2500100994).

Keywords: hydromorphone, intrathecal anesthesia, anorectal surgery, postoperative analgesia, randomized controlled trial

Introduction

Anorectal diseases refer to a spectrum of disorders affecting the anus and rectum, including hemorrhoids, perianal pruritus, anal fissures, functional rectal pain, perianal abscesses, condyloma acuminatum, rectal prolapse, and fecal incontinence.[1] Among these, conditions such as hemorrhoids, anal fissures, and anal abscesses are highly prevalent worldwide.[2] Currently, surgical intervention is the primary treatment for these conditions. However, due to the rich and complex innervation and vascular supply of the perianal region, which is highly sensitive to pain, patients often experience severe postoperative pain.[3,4] Although various analgesic strategies, such as patient-controlled analgesia, oral analgesics, and local infiltration anesthesia, are employed, managing pain after surgery remains challenging, especially during dressing changes and defecation.[4]

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Inadequate perioperative pain control may increase the risk of complications, including nausea, intestinal obstruction, delayed mobilization, prolonged hospitalization, and chronic pain syndromes.[2] Furthermore, patients undergoing short-term anorectal procedures are typically discharged within two to three days after surgery, making postoperative pain after discharge easily overlooked by clinicians.[5] This often results in insufficient analgesia and decreased patient satisfaction. Therefore, there is a compelling need to optimize analgesic protocols to facilitate recovery and improve patient outcomes.

Intrathecal anesthesia with local anesthetics is commonly used in anorectal surgery due to its benefits, including shorter recovery time, reduced postoperative pain scores, and decreased demand for analgesics in the recovery unit.[6] The addition of low-dose opioids to intrathecal local anesthetics represents an attractive option for enhancing postoperative analgesia, as it enables effective pain control with lower total drug doses compared to systemic opioid administration.[7] Morphine and fentanyl are widely employed as adjuvants in this setting, with well-established roles in prolonging analgesic duration, reducing opioid consumption, and attenuating pain intensity. However, the use of intrathecal morphine is associated with frequent adverse effects such as nausea, vomiting, pruritus, and respiratory depression. Conversely, the highly lipophilic nature of fentanyl limits its duration of extended analgesia.[8] These drawbacks constrain their utility in intrathecal regimens. Therefore, there is a need to explore alternative analgesic agents or strategies that can provide adequate postoperative pain relief while minimizing drug-related adverse effects.

Hydromorphone is an opioid with pharmacodynamic properties intermediate between morphine and fentanyl. It is more potent than morphine but less so than fentanyl, thus providing a unique advantage in its dose-response profile. Compared to morphine, its differing hydrophilicity-lipophilicity balance may contribute to a differentiated adverse effect profile.[9] Evidence from a randomized crossover study in healthy volunteers suggests that hydromorphone may offer a more favorable clinical profile than morphine in terms of analgesic efficacy and side effects.[10] In contrast to fentanyl, hydromorphone exhibits higher bioavailability, and some studies indicate a lower incidence of adverse events, potentially resulting in a more advantageous analgesia-to-side-effect balance.[11] These properties theoretically support hydromorphone as a suitable candidate for intrathecal administration and may facilitate its use within enhanced recovery after surgery (ERAS) protocols.

Nevertheless, effective perioperative pain management remains a challenge in anesthesiology. Although hydromorphone is an established and well-tolerated intrathecal opioid, clinical evidence specifically in the context of anorectal surgery is scarce, and high-quality prospective evidence is particularly lacking. Existing research has primarily focused on other surgical settings and pain conditions,[12–15] leaving the analgesic benefits and risks of hydromorphone in anorectal procedures unclear. Therefore, we designed this prospective, randomized, double-blind, controlled trial to systematically evaluate the effect of intrathecal hydromorphone on postoperative analgesia in patients undergoing anorectal surgery, with the aim of providing reliable evidence for clinical practice and ERAS protocols.

Materials and Methods

Objective

The primary objective of this study is to assess the effect of intrathecal hydromorphone on postoperative analgesia duration and Numeric Rating Scale (NRS) pain scores in patients undergoing benign anorectal surgery. Secondary objectives include comparing the incidence of adverse events, supplemental opioid consumption, and patient satisfaction between groups.

Study Design and Setting

This study employs a prospective, randomized, double-blind, controlled trial design (PROBE design). A total of 76 patients undergoing benign anorectal surgery at Deyang People's Hospital between July 2025 and December 2026 will be enrolled. Participants will be allocated via a computer-generated random sequence to either the intervention group H (intrathecal ropivacaine 10 mg + hydromorphone 75 μg) or the control group C (intrathecal ropivacaine 10 mg). Group assignment will be concealed using sealed, opaque envelopes. The study protocol has been approved by the Ethics Committee of Deyang People's Hospital (Approval No.: 2025-04-024-K01) and registered with the Chinese Clinical Trial Registry (Registration No.: ChiCTR2500100994). The trial will be conducted in strict accordance with the SPIRIT guidelines. Figures 1 and 2 show the study timeline and flowchart, respectively.

Time Point	Enrollment	Allocation	Operation	Postoperation					
				4h	6h	8h	10h	12h	24h
Enrollment									
Eligibility screening	x								
Informed consent	x								
Allocation		x							
Interventions									
Hydrocodone+Ropivacaine			x						
Ropivacaine			x						
Assessments									
Demography	x								
ASA classification	x								
Disease diagnosis	x								
Type/duration of surgery		x							
Intraoperative medication		x							
Duration of analgesia				←	—	—	—	—	→
NRS Pain score				←	—	—	—	—	→
RASS score				←	—	—	—	—	→
Adverse reactions				←	—	—	—	—	→
Opioid consumption									x
Patient satisfaction									x

Figure 1 Study timeline.
Abbreviations: ASA, American Society of Anesthesiologists; NRS, Numeric Rating Scale; RASS, Richmond Agitation-Sedation Scale.

Eligibility Criteria

Patients scheduled for surgical treatment of benign anorectal diseases (such as hemorrhoids, anal fissures, anal fistula, perianal abscess, or condyloma acuminatum) will be considered for inclusion. Additional inclusion criteria comprise: age ≥18 years and ASA physical status I–III. Exclusion criteria include: known allergy or intolerance to the study drugs; history of chronic pain or regular use of analgesics preoperatively; coagulation disorders or current anticoagulant medication; previous spinal trauma or surgery; conversion to general anesthesia due to failed intrathecal block; or unwillingness to cooperate with the protocol.

Dropout Criteria

Participants will be withdrawn from the study under any of the following conditions: clinical deterioration or occurrence of a serious adverse event; severe drug-related adverse reaction; patient request to withdraw or decline further participation; or any other reason deemed appropriate by the investigators.

Participant Eligibility and Consent

Eligible patients will be identified by investigators based on the predefined criteria. These individuals will then receive both written and oral information about the study and will be enrolled after providing written informed consent.

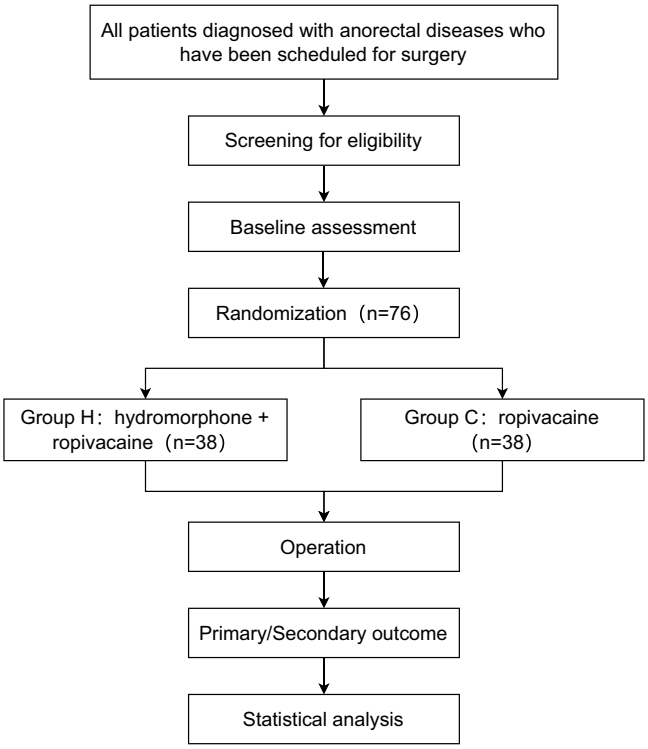

Figure 2 Flowchart of this study.

Randomization and Blind Methods

The randomization sequence will be generated by a research team member not involved in patient recruitment or clinical evaluation using the online service www.sealedenvelope.com. The parameters will be set as follows: a total sample size (N=76), block randomization with block sizes of 4 and 6 to enhance baseline comparability between groups, and a 1:1 allocation ratio to either the intrathecal hydromorphone plus ropivacaine group (Group H) or the intrathecal ropivacaine group (Group R). To ensure strict allocation concealment, each allocation outcome (H or R) will be placed in sequentially numbered, opaque, sealed envelopes, or the allocation concealment feature within the online tool will be used. The allocation for an eligible patient will be disclosed sequentially by designated personnel only upon enrollment. Investigators, anesthesiologists, the surgical team, and follow-up personnel will remain blinded to the allocation sequence throughout the trial to maintain the double-blind design.

Prior to study initiation, an anesthesia nurse not involved in the trial will open the envelopes and prepare the study drugs. For patients in Group H, hydromorphone hydrochloride injection (2 mL: 2 mg; Yichang Humanwell Pharmaceutical Co., Ltd., Yichang, Hubei, China) will first be diluted to a concentration of 0.1 mg/mL. Then, 0.75 mL of this solution will be drawn into a 1 mL syringe and transferred to a 2.5 mL syringe, followed by the addition of 1 mL of 1% ropivacaine hydrochloride injection (10 mL: 100 mg; Ruiyang Pharmaceutical Co., Ltd., Yiyuan, Shandong, China) and 0.25 mL of normal saline, resulting in a total volume of 2 mL. For patients in Group C, 1 mL of 1% ropivacaine will be mixed with 1 mL of normal saline in a 2.5 mL syringe, also yielding a total volume of 2 mL. This pharmaceutical blinding protocol ensures scientific rigor, impartiality, and protection of participant safety and rights.

Study Procedure

On the day of surgery, an intravenous line will be established in the preoperative preparation area, and lactated Ringer's solution will be administered. Upon entering the operating room, all patients will be placed under standard monitoring, including electrocardiography, non-invasive blood pressure, and pulse oximetry. With the patient in the left lateral position, subarachnoid puncture will be performed at the L3–L4 interspace. After confirming free flow of clear cerebrospinal fluid,

patients in Group H will receive an injection of 10 mg ropivacaine combined with 75 μg hydromorphone in normal saline (total volume 2 mL) directed cephalad at a rate of 0.2 mL/s. Patients in Group C will receive 10 mg ropivacaine in normal saline (total volume 2 mL) injected under the same conditions. All intrathecal medications will be prepared prior to anesthesia by an anesthesia nurse not involved in the study. The same surgical team or a single expert surgeon will perform all procedures. During surgery, metaraminol will be administered as needed to maintain blood pressure within 20% of baseline values. If heart rate drops below 50 beats per minute, atropine will be administered.

All patients will receive standardized postoperative care, including multimodal analgesia, management of nausea and pruritus, continuous monitoring, and emergency interventions as required. To ensure that the primary outcome, the time to first request for rescue analgesia, specifically reflects the cessation of the neuraxial block's effect, the following standardized protocol will be implemented. When a patient complains of pain and requests analgesia, a researcher blinded to group assignment will conduct a bedside assessment to confirm whether the patient's resting Numeric Rating Scale (NRS) pain score is 4 or higher. Upon meeting this threshold, rescue analgesia will be administered as oral oxycodone, with a dose of 5 mg for an NRS score of 4–6 or 10 mg for an NRS score of ≥7, repeated as needed every 12 hours. For nausea, ondansetron (4 mg, IV) will be available as needed. Pruritus will be treated with diphenhydramine (25 mg, IV or orally, every 6 hours as needed). In cases of respiratory depression (respiratory rate <8 breaths per minute or SpO_2 <94%) or excessive sedation (a Richmond Agitation-Sedation Scale [RASS] score of −3, −4, or −5), naloxone (0.2 mg, IV) will be administered. The RASS is a 10-point scale used to assess the level of consciousness, with anchors ranging from +4 (combative) to −5 (unarousable).

The duration of postoperative analgesia, NRS pain scores at various time points, total opioid consumption within 24 hours postoperatively, the incidence of adverse effects, and patient satisfaction will be recorded.

Outcomes

The primary outcome will be the duration of postoperative analgesia following intrathecal anesthesia. Key secondary outcomes will include pain scores assessed at multiple time points. We will also record postoperative adverse effects (including nausea, vomiting, pruritus, and sedation levels), 24-hour opioid consumption, and patient satisfaction. All data will be collected by blinded investigators through patient interviews at 4, 6, 8, 10, 12, and 24 hours after intrathecal administration.

The duration of analgesia is defined as the time from intrathecal injection to the first documented request for rescue analgesia due to a pain score ≥ 4. Pain scores will be assessed using the Numeric Rating Scale (NRS), where 0 indicates "no pain" and 10 represents "the worst pain imaginable".[16]

The level of sedation will be assessed using the Richmond Agitation-Sedation Scale (RASS), with excessive sedation defined as a RASS score of –2 or less.[17] The severity of nausea and pruritus will be graded based on patient self-reporting using a 4-point scale where 0 indicates none, 1 mild, 2 moderate, and 3 severe.

Opioid consumption will be extracted from patients' electronic medical records. Patient satisfaction will be assessed using a questionnaire rated on a 5-point scale: 0 = dissatisfied, 1 = slightly satisfied, 2 = neutral, 3 = slightly dissatisfied, and 4 = satisfied. Additionally, treatments for nausea or pruritus and the management of hypoventilation events (respiratory rate <8 breaths/min or SpO_2 <94%) within 24 hours after intrathecal anesthesia will be recorded.

Quality Control and Data Management

Prior to trial initiation, a clinical investigation manual will be developed, and all investigators will receive comprehensive training to ensure adherence to the study protocol and consistency in outcome assessment. Data will be prospectively collected using an electronic Case Report Form (eCRF), which captures patient baseline information (demographics, ASA classification, disease diagnosis), perioperative records (surgical type, duration, intraoperative medications), and outcome measures. All data will be entered by trained research staff at predetermined time points: preoperatively, intraoperatively, and during postoperative follow-up. To ensure confidentiality, personally identifiable information will be linked to study data through unique codes and stored separately.

Statistics

The sample size was calculated based on the following rationale. Based on preliminary data and relevant literature, the expected duration of analgesia for the control group (intrathecal ropivacaine alone) is approximately 4 ± 1.5 hours (mean ± SD).[18] We hypothesize that the hydromorphone group will achieve a 1-hour prolongation in analgesic duration (representing a 25% relative increase from the baseline). This effect size is considered clinically meaningful, as its magnitude is comparable to the well-established standard in pain research where a reduction in pain intensity of approximately 30% is regarded as a minimal clinically important difference.[19] With a two-sided α of 0.05, a power (1 – β) of 0.8, and a 1:1 allocation ratio, 36 patients per group are required. Accounting for an estimated dropout rate of 5%, a minimum of 38 participants per group will be included, resulting in a total sample size of 76 patients.

Continuous data will be assessed for normality using the Shapiro–Wilk test and for homogeneity of variances using Levene's test. If both assumptions are met, independent samples *t*-tests will be used for between-group comparisons, with results presented as mean ± standard deviation. Otherwise, the Mann–Whitney *U*-test will be employed, with results presented as median and interquartile range. Categorical data will be summarized as frequency (percentage) and compared using the Chi-square test or Fisher's exact test, as appropriate.

Specifically, for the primary outcome (duration of analgesia), a between-group comparison will be performed using the method described above, with a significance level (α) set at 0.05. For secondary outcomes, pain scores (NRS) at different postoperative time points will be compared between groups at each time point. To account for multiple comparisons, the Bonferroni correction will be applied, resulting in an adjusted significance level of 0.0083. The total 24-hour opioid consumption and patient satisfaction scores will be analyzed as continuous data, while the incidence of adverse effects will be analyzed as categorical data. The significance level for these secondary outcome comparisons (excluding the corrected NRS scores) is set at 0.05. All statistical analyses will be performed using SPSS software (version 26.0).

Discussion

Surgery is an effective treatment for anorectal diseases; however, it often causes severe postoperative pain due to the dense sensory innervation of the anal region.[2] Studies have shown that more than 60% of patients still experience moderate-to-severe pain within the first 7 days after surgery.[5] Such persistent pain can limit mobility, increase complication rates, prolong hospitalization, and reduce quality of life, underscoring the critical importance of effective analgesia.[20] Clinical practice guidelines recommend multimodal analgesia regimens for patients undergoing anorectal surgery. Nevertheless, prospective cohort studies indicate that even with standard multimodal approaches, including local anesthetic infiltration and systemic oral analgesics, a considerable proportion of patients continue to report high pain scores.[4] These findings emphasize the need for further investigation into combined analgesic strategies and extended follow-up assessments.

Intrathecal anesthesia is widely used for pain management in anorectal surgery. The addition of low-dose opioids to intrathecal anesthetics can prolong postoperative analgesia and reduce analgesic requirements, with morphine and fentanyl being frequently employed.[6] However, intrathecal morphine is often associated with adverse effects such as nausea/vomiting, pruritus, urinary retention, and potential respiratory depression, while intrathecal fentanyl carries a risk of pruritus and offers limited duration of analgesia.[21,22] These limitations constrain their clinical utility.

Hydromorphone, a semi-synthetic opioid, exhibits intermediate lipophilicity and hydrosolubility.[23] Compared to morphine, its higher lipid solubility may contribute to a reduced incidence of side effects.[9] A comparative study in cancer patients demonstrated that intrathecal hydromorphone resulted in fewer adverse events than intrathecal morphine.[12] In contrast to fentanyl, its moderate hydrophilicity may provide advantages in terms of analgesic efficacy, duration of action, and adverse event profile.[11] Owing to its balanced pharmacodynamic properties between lipophilicity and hydrophilicity, hydromorphone shows potential for an improved balance between analgesic potency and side effects, positioning it as a promising candidate for intrathecal analgesia. Further investigation is warranted to evaluate its efficacy and safety in the context of anorectal surgery.

Research on intrathecal hydromorphone dosing has primarily focused on obstetric anesthesia. Studies in this field have demonstrated an approximate potency ratio of 2:1 between intrathecal morphine and hydromorphone, suggesting that 75 μg of intrathecal hydromorphone can provide adequate postoperative analgesia with a manageable side effect

profile.[14,15] Furthermore, a retrospective study on intrathecal hydromorphone for post-abdominal surgery analgesia found no significant differences in 24-hour pain incidence or risk of serious adverse events across different dosages after adjusted analysis.[7] Given that anorectal surgeries are confined to the perineal region, with nerve innervation typically lower than that of the lower abdominal incision in cesarean sections, it is theorized that 75 μg of intrathecal hydromorphone may suffice for postoperative analgesia in this context. However, its precise efficacy and safety profile require further validation in the current study.

Nausea/vomiting and pruritus are the most common adverse effects associated with intrathecal opioid administration, while excessive sedation and respiratory depression represent the most critical safety concerns. To ensure patient safety, the current study protocol incorporates systematic monitoring of adverse events, vital signs, and sedation depth at each postoperative follow-up time point. Standardized intervention measures have been established. Specifically, ondansetron for nausea/vomiting and diphenhydramine for pruritus. In the event of severe complications, such as respiratory rate <8 breaths/min or SpO_2 <94%, prompt oxygen therapy and titrated naloxone administration will be initiated. All interventions are supported by comprehensive emergency equipment available in the ward (including naloxone and airway management devices) and an anesthesia emergency support system, with the goal of maximizing patient safety and facilitating the implementation of ERAS protocols.

Despite the rigorous design, several limitations of this study merit consideration. First, the single-center design. All data were derived from a single institution, which, while ensuring consistency in procedures and assessments, may limit the generalizability of the findings. Future multi-center studies are warranted to validate the results. Second, the selective patient population. The study exclusively included patients undergoing elective benign anorectal surgery, excluding those with malignancies or complex anorectal conditions (eg, reoperations, complex fistulas). This enhances internal homogeneity and facilitates a clearer evaluation of the intervention but may restrict the direct applicability of the conclusions to a broader spectrum of anorectal surgical patients. Third, measurement and individual variability. Although standardized tools were used to assess analgesic efficacy and adverse effects, outcomes may still be influenced by individual differences, subtle surgical variations, and subjective patient reporting, despite the implementation of blinded assessments to mitigate bias.

Although intrathecal hydromorphone has demonstrated benefits in cancer pain management and postoperative analgesia following abdominal and obstetric surgeries, high-quality evidence regarding its efficacy and safety in anorectal procedures remains limited. To address this gap, we designed a randomized, double-blind, controlled trial to evaluate the analgesic efficacy and safety profile of intrathecal hydromorphone combined with ropivacaine in patients undergoing anorectal surgery. The study employs a rigorous methodology, including strict inclusion/exclusion criteria and a predefined unblinding protocol, to ensure patient safety and safeguard study integrity. It is anticipated that the findings will provide valuable evidence to optimize postoperative pain management strategies for this specific surgical population.

Trial Status

The trial is currently ongoing; patient recruitment commenced on October 1, 2025 and is expected to be completed by March 31, 2026.

Data Sharing Statement

Data are available from the corresponding author upon reasonable request.

Ethics and Dissemination

The trial will be conducted in accordance with the Declaration of Helsinki. The study protocol has been approved by the Ethics Committee of Deyang People's Hospital (Approval No.: 2025-04-024-K01) and registered with the Chinese Clinical Trial Registry (Registration No.: ChiCTR2500100994). All participant information will be anonymized and kept strictly confidential, and participants retain the right to withdraw from the trial at any time. The results of this study will be submitted for publication in a peer-reviewed journal and presented at relevant academic conferences.

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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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