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Metoclopramide for Preventing Ileus after Benign Gynecologic Surgery: A randomized controlled trial

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ABSTRACT

Objectives: To assess the efficacy of metoclopramide in preventing ileus after benign gynecologic surgery.

Materials and Methods: Participants included were diagnosed with benign gynecologic conditions and scheduled for abdominal hysterectomy at Khon Kaen Hospital between October 2021 and May 2022. Participants were randomly allocated into two groups: the metoclopramide group (n=25) received an injection of 2 ml (10 mg) of intramuscular metoclopramide, while the control group (n=25) received an injection of normal 2 ml of intramuscular saline at 2 h after surgery.

Results: The metoclopramide group had significantly less time to first passage of flatus than the control group (placebo) (1,785.3 ± 125.7 vs. 2,186.3 ± 103.0 min, mean difference 401.0 min (95% CI 73.1 to 728.9, p=0.02)). The incidence of ileus symptoms was significantly lower in the metoclopramide group than in the control group (28% vs 68%, p<0.01). Although not statistically significant, the metoclopramide group compared to the control group experienced (a) a shorter time to first defecation and time to tolerate a solid diet, (b) less need for additional antiemetics and additional analgesics, and (c) a shorter length of hospital stay. There were no adverse effects related to the use of metoclopramide in this study.

Conclusion: Postoperative intramuscular metoclopramide enhanced the recovery of bowel function after benign gynecologic surgery.

Keywords: metoclopramide, benign gynecologic surgery, postoperative ileus.

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การใช้ยาเมโทโคลพราไมด์ในการป้องกันการเกิดภาวะลำไส้อืดหลังการผ่าตัดโรคทางนรีเวชที่ไม่ใช่มะเร็ง : การศึกษาแบบสุ่ม

ชัยณรงค์ ศิลปษา, รุ่งฤดี จีระทรัพย์, ทุมวดี ตั้งศิริวัฒนา

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพของยาเมโทรโคลพลาไมด์ในการป้องการเกิดภาวะลำไส้อืดหลังการผ่าตัดโรคทางนรีเวชที่ไม่ใช่มะเร็ง*

วัสดุและวิธีการ: *อาสาสมัครผู้เข้าร่วมที่ได้รับการวินิจฉัยโรคทางนรีเวชที่ไม่ใช่มะเร็ง และมีกำหนดการผ่าตัดมดลูกทางหน้าท้องที่โรงพยาบาลขอนแก่น ระหว่างเดือน ตุลาคม พ.ศ.2564 ถึง พฤษภาคม พ.ศ. 2565 ได้รับการสุ่มแบ่งอาสาสมัครเป็นสองกลุ่ม คือกลุ่มเมโทโคลพราไมด์จำนวน 25 คน ได้รับยาเมโทโคลพราไมด์ ปริมาณ 2 มิลลิลิตร (ขนาด 10 มิลลิกรัม) แบบฉีดทางกล้ามเนื้อ ในขณะที่กลุ่มควบคุมจำนวน 25 คน ได้รับน้ำเกลือปริมาณ 2 มิลลิลิตร แบบฉีดทางกล้ามเนื้อ ที่สองชั่วโมงหลังผ่าตัด*

ผลการศึกษา: *กลุ่มเมโทโคลพราไมด์มีระยะเวลาการผายลมครั้งแรกหลังการผ่าตัดน้อยกว่ากลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติ (1,785.3 ± 125.7 vs. 2,186.3 ± 103.9 นาที, mean difference 401.0 นาที (95% CI 73.1 to 728.9; p = 0.02) อุบัติการณ์ผู้ป่วยที่มีภาวะลำไส้อืดหลังการผ่าตัดลดลงอย่างมีนัยสำคัญในกลุ่มที่ได้ยาเมโทโคลพราไมด์เมื่อเทียบกับกลุ่มควบคุม (ร้อยละ 28% vs. 68; p < 0.01) กลุ่มเมโทโคลพราไมด์มีระยะเวลาในการเริ่มขับถ่ายอุจจาระ, การสามารถเริ่มรับประทานอาหารที่เคี้ยวได้, การใช้ยาแก้คลื่นไส้อาเจียน, การใช้แก้ปวดเพิ่ม และระยะเวลาในการพักรักษาตัวโรงพยาบาลน้อยกว่ากลุ่มควบคุม แต่ไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติ ไม่พบผลข้างเคียงที่สัมพันธ์กับการใช้ยาเมโทโคลพราไมด์ในการศึกษานี้*

สรุป: *การได้รับยาเมโทโคลพราไมด์แบบฉีดทางกล้ามเนื้อหลังผ่าตัดช่วยกระตุ้นการทำงานของสำไส้หลังการผ่าตัดโรคทางนรีเวชที่ไม่ใช่มะเร็ง*

คำสำคัญ: *ยาเมโทโคลพราไมด์, การผ่าตัดโรคทางนรีเวชที่ไม่ใช่มะเร็ง, ภาวะลำไส้อืดหลังการผ่าตัด*

Introduction

Postoperative ileus (POI) is a transient impairment of gastrointestinal function[1]. POI usually presents with nausea, vomiting, abdominal pain, abdominal distention, bloating, and constipation[1,2] and may be followed by aspiration, dehydration, electrolyte imbalance, and hospital-acquired infection[1,2]. POI is a public health problem that often occurs after abdominal surgery. The respective incidence of POI in abdominal surgery and gynecological cancer surgery was 10-30%[1] and 51.8%[3]. If POI is longer than the presumed normal duration, it is assumed that a pathological or prolonged POI has occurred[1], increasing the cost of treating complications and the length of hospital stay.

The pathophysiology of POI is complex, which may result from the stimulation of the autonomic nervous system during surgical procedures and the release of various neurotransmitters or cytokines that activate inflammatory processes, resulting in the cessation of intestinal function. After surgery, the gastrointestinal system resumes normal function by reducing the inflammatory process and stimulating a cholinergic effect through the vagus nerve[1,2,4]. Based on the pathophysiology that occurs in the intestines during surgery, there are multiple methods to prevent POI, such as bowel preparation, prophylactic nasogastric tube insertion, minimally invasive surgery, maintenance of euvolemia during operation, multimodal analgesia, alvimopan (opioid μ-receptor antagonist), prokinetics, coffee, gum chewing, and early postoperative feeding[1,2,4,5].

Metoclopramide is classified as a prokinetic—part of a group discovered in the 1950s[6,7]. It acts as a dopamine D2 receptor antagonist, a 5-hydroxytryptamine 4 receptor agonist (serotonin) and muscarinic receptor agonist[4, 6, 7]—all of which facilitate cholinergic activity within the enteral nervous system or the vagus nerve. The effects on the digestive system include reducing nausea and vomiting, increasing contraction of the esophageal sphincter, increasing peristalsis, and reducing gastric emptying time[4,7]. According to its effects on the gastrointestinal system, several trials studied the effect of metoclopramide on preventing POI; however, its efficacy remains uncertain[1]. Previous studies found positive and negative results vis-à-vis preventing the occurrence of POI[1, 8, 9, 10, 11], so the current study aimed to evaluate the efficacy of metoclopramide in preventing POI after benign gynecologic surgery.

Materials and Methods

This randomized controlled study was conducted at the Department of Obstetrics and Gynecology, Khon Kaen Hospital. Before the commencement of the research, its protocol was reviewed and approved by the Khon Kaen Hospital Institutional Review Board for Human Research (reference number: KEF64019).

Recruited patients included those diagnosed with benign gynecological conditions and scheduled for abdominal hysterectomy with or without adnexal surgery. Patients were excluded if they (a) had conditions that might influence gastrointestinal motility (including previous bowel surgery, previous abdominal irradiation, chronic constipation, pancreatitis, peritonitis, hypothyroidism, and chronic use of drugs that impact intestinal peristalsis), (b) used oral or mechanical bowel preparation before surgery, (c) had a history of serious side effects due to metoclopramide, (d) underwent a procedure with entry into the gastrointestinal tract or bowel anastomosis, and/or (e) needed intensive care after surgery or nasogastric tube drainage. The patients were informed about the study at the gynecological ward before undergoing surgery. Written informed consent was obtained from each participant before enrollment. Postoperative hysterectomy women who met the eligibility criteria were randomly assigned into two groups using a computer-generated list and allocation concealment using sequentially opaque envelopes: the metoclopramide group and the control group. Baseline characteristics were recorded: age, body mass index (BMI), comorbid diseases, indications for surgery, previous abdominal surgery, and preoperative hemoglobin (Hb) level. The participants were informed

about the outcomes that they had to observe and record, including: time to first passage of flatus after surgery, time to first defecation, and ileus symptoms. A digital clock was set up as the standard time for recording the outcomes. Before the operation, all patients received the same preoperative care, anesthetic protocol, intravenous antibiotic prophylaxis after induction of anesthesia, and transverse abdominis plane (TAP) block. The surgical procedures were performed by staff or senior residents under supervision by staff not involved in the study.

After the operation, the nurse on the ward opened the envelope that contained a 3-ml syringe. Each identical syringe had 2 ml of clear liquid of metoclopramide or normal saline prepared by a pharmacologist. The metoclopramide group received 2 ml (10 mg) of intramuscular metoclopramide (MET-SIL®, T.P. DRUG LABORATORIES (1969) CO., LTD), while the control group received 2 ml of intramuscular normal saline (placebo) 2 h after surgery. The surgeon and ward nurses did not know which agent the participants received.

The postoperative care protocol was intravenous administration of an opioid agent (2 mg of morphine for body weight < 50 kg or 3 mg for body weight ≥ 50 kg) every 4 h for 24 h. In addition, a single dose of 4 mg intravenous ondansetron was administered to prevent nausea and vomiting. Prophylactic antibiotics were administered for 24 h after surgery. Ambulation was promoted the day after surgery. The postoperative feeding regimen was standardized; a liquid/soft diet was begun on the first postoperative day, followed by a solid/regular diet over the next 24 h, as tolerated.

When the patients began postoperative feeding, additional analgesics were provided according to the patient numeric pain score (1-10). For example, oral paracetamol 500 mg or Ibuprofen 400 mg were provided when the pain score was 4 – 6 out of 10, while intravenous morphine was provided when the pain was ≥ 7 out of 10.

All primary and secondary outcomes were recorded. The primary outcome was time to first passage of flatus after surgery. The secondary outcomes were time to first defecation, time to tolerate a solid diet (defined as eating any food that requires chewing without vomiting or nausea within 4 h after the meal), additional antiemetic requirements, additional analgesic requirements, ileus symptoms (defined by the I-FEED scoring system[5] divided into three categories: normal or mild [score 0-2], moderate or postoperative gastrointestinal intolerance [score 3-5], severe or postoperative gastrointestinal dysfunction [score > 6]), adverse effect of metoclopramide (e.g., drowsiness, restlessness, extrapyramidal reaction, and/or rash)[11], and length of hospital stay. After the patients became conscious, the outcomes were reviewed and then recorded in the record form by the ward nurse every 4 h after surgery until the patient was discharged. Patients could be discharged when they could tolerate a solid diet and urinate and defecate normally, had no bleeding per vagina, had no abdominal pain, could ambulate without assistance, had stable vital signs without fever for at least 24 hours, and had no postsurgical complications. After discharge, the length of hospital stay was recorded.

The sample size was calculated based on a pilot study of 30 patients with a power of 90%, an α level of 0.05, and a dropout rate of 15%. Fifty participants (25 in each group) were thus required. Data were analyzed using Stata version 14 based on an intention-to-treat analysis. The normality of continuous data was tested using histogram plots and/or the Kolmogorov-Smirnov test of normality. Student's t-test (or the Mann-Whitney U test) and the chi-squared test (or Fisher's exact test) were used to analyze continuous and categorical data, respectively. The Kaplan Meier survival analysis was used to analyze time to first passage of flatus after surgery. A p value < 0.05 was considered statistically significant.

Results

Between October 2021 and May 2022, 53 eligible women scheduled for abdominal hysterectomy, with or without adnexal surgery, were enrolled in the

study. Three of them were excluded from the study: one because the surgery was canceled due to covid-19 infection and two because of postoperative complications requiring intensive care. So, a total of 50 eligible women were randomly assigned: 25 to the metoclopramide group and 25 to the control group. There were no dropouts (Fig. 1). Preoperative baseline characteristics were similar between groups, including age, body mass index (BMI), comorbid diseases, indications for surgery, previous abdominal surgery, and pre-operative hemoglobin (Hb) level (Table 1).

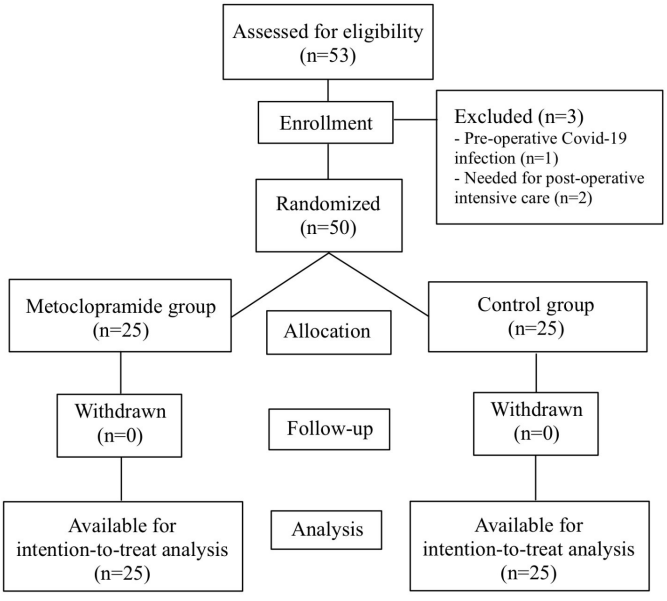

Fig. 1. Study flow.

Table 1. Baseline characteristics of participants undergoing abdominal hysterectomy for benign gynecologic condition.

Baseline characteristic	Metoclopramide group (n=25)	Control group (n=25)	p value
Age (years), mean (SD)	47.3 (5.8)	49.2 (7.2)	0.30[a]
Body mass index (kg/m^2), mean (SD)	26.7 (5.8)	25.9 (4.7)	0.59[a]
Comorbid diseases, n (%)	6 (24.0)	6 (24.0)	1.00[b]
Indication for surgery, n (%)			0.08[c]
Myoma uteri	23 (92.0)	15 (60.0)	
Adenomyosis	1 (4.0)	5 (20.0)	
Cervical intraepithelial neoplasia III	0 (0.0)	1 (4.0)	
Endometrial hyperplasia	0 (0.0)	2 (8.0)	
Ovarian tumor	1 (4.0)	2 (8.0)	
Previous abdominal surgery, n (%)	13 (52.0)	14 (56.0)	0.77[b]
Pre-operative hemoglobin level (g/dL), mean (SD)	10.2 (2.4)	11.6 (1.9)	0.28[a]

[a] Student T-test, [b] Chi-square test, [c] fisher's exact test. SD: standard deviation.

Operative outcomes were also similar between groups, including operative procedure, type of incision, length of incision, operative time, duration of anesthesia, estimated blood loss, provisional diagnosis, and post-operative hemoglobin (Hb) level (Table 2).

Table 2. Operative outcomes of participants undergoing abdominal hysterectomy for benign gynecological condition.

Operative outcome	Metoclopramide group (n=25)	Control group (n=25)	p value
Operative procedure, n (%)			0.10[b]
Total abdominal hysterectomy with bilateral salpingectomy	9 (36.0)	4 (16.0)	
Total abdominal hysterectomy with bilateral salpingo-oophorectomy	16 (64.0)	21 (84.0)	
Type of incision, n (%)			
Low Midline	9 (36.0)	13 (52.0)	0.25[b]
Pfannenstiel	15 (60.0)	12 (48.0)	0.39[b]
Maylard	1 (4.0)	0 (0.0)	0.50[c]
Length of incision (cm), mean (SD)	11.3 (1.2)	11.8 (1.6)	0.25[a]
Operative time (min), mean (SD)	86.2 (25.8)	91.1 (22.6)	0.48[a]
Duration of anesthesia (min), mean (SD)	106.0 (36.6)	109.2 (22.3)	0.71[a]
Estimated blood loss (ml), mean (SD)	165.6 (27.8)	147.2 (26.0)	0.63[a]
Post-operative diagnosis, n (%)			0.08[c]
Myoma uteri	23 (92.0)	15 (60.0)	
Adenomyosis	1 (4.0)	5 (20.0)	
Cervical intraepithelial neoplasia III	0 (0.0)	1 (4.0)	
Endometrial hyperplasia	0 (0.0)	2 (8.0)	
Ovarian tumor	1 (4.0)	2 (8.0)	
Post-operative hemoglobin level (g/dL), mean (SD)	9.8 (1.9)	11.2 (1.6)	0.07[a]

[a] Student T-test, [b] Chi-square test, [c] fisher's exact test. SD: standard deviation.

The respective time to first passage of flatus after surgery was 1,785.3 ± 125.7 min and 2,186.3 ± 103.9 min in the metoclopramide group and control group, respectively. The mean difference was 401.0 min (95% confidence interval (CI) 73.1 to 728.9, p = 0.02). The respective proportion to first passage of flatus within 48 h after surgery in the metoclopramide and control group was 100% and 88%, respectively. The respective mean difference in minimum and maximum time to first passage of flatus was 815 and 145 min (Table 3). The Kaplan-Meier survival analysis of time to first passage of flatus between groups is presented in Fig. 2. The respective median survival time to first passage of flatus after surgery (50%) in the metoclopramide group and control group was 1,530 min (95% CI: 1,435 to 2,365) vs. 2,085 min (95% CI: 1,715 to 2,640, p = 0.02).

Table 3. Postoperative ileus (POI), additional drug requirement and length of hospital stay of participants undergoing abdominal hysterectomy for benign gynecological condition.

Outcomes	Metoclopramide group (n=25)	Control group (n=25)	Mean Difference (min)	95% CI	p value
Time to first passage of flatus (min), mean (SD)	1,785.3 (125.7)	2,186.3 (103.9)	401.0	73.1 to 728.9	0.02[a]*
Minimum time (min)	610	1425	815		
Maximum time (min)	2880	3025	145		
At 12 h, n (%)	2 (8)	0 (0)			
At 24 h, n (%)	8 (32)	1 (4)			
At 36 h, n (%)	16 (64)	13 (52)			
At 48 h, n (%)	25 (100)	22 (88)			
More than 48 h, n (%)		25 (100)			
Time to first defecation (min), mean (SD)	1,767.0 (322.1)	1,949.0 (435.4)	182.0	-35.8 to 399.8	0.09[a]
Time to tolerate a solid diet (min), mean (SD)	4,022.7 (928.9)	4,077.4 (1,202.9)	54.7	-556.4 to 665.9	0.85[a]
Additional antiemetic requirements, n (%)	2 (8.0)	3 (12.0)			0.63[b]
Additional analgesic requirements, n (%)	10 (40.0)	11 (44.0)			0.77[b]
Ileus symptoms, n (%)	7 (28.0)	17 (68.0)			< 0.01[b]*
Severe	0 (0.0)	1 (4.0)			0.50[c]
Moderate	1 (4.0)	6 (24.0)			0.04[b]*
Mild	6 (24.0)	10 (40.0)			0.22[b]
Length of hospital stay (hrs.), mean (SD)	99.8 (8.4)	100.6 (6.7)			0.74[a]

[a] Student T-test, [b] Chi-square test, * significant p<0.05. SD: standard deviation, CI: confidence interval.

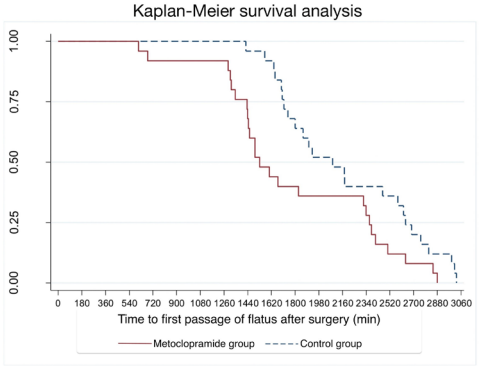

Fig. 2. Kaplan-Meier survival analysis of the time to first passage of flatus

Kaplan-Meier survival estimated the time to first passage of flatus. Median time to first flatus (50%) of metoclopramide group was 1,530 min (95% CI: 1,435 to 2,365) and control group was 2,085 min (95% CI: 1,715 to 2,640). Log-rank test for survivor functions (p = 0.02)

In addition, ileus symptoms were significantly less frequent in the metoclopramide group (n = 7, 28%) than in the control group (n = 17, 68%). The ileus symptoms were categorized using the I-FEED scoring system. Moderate symptoms were defined as postoperative gastrointestinal intolerance (POGI), and these increased significantly in the control group compared to the metoclopramide group (24% vs. 4%, p = 0.04). None of the patients with ileus symptoms had any clinicals indicating mechanical obstruction or peritonitis and responded to supportive treatment. Whereas time to first defecation, time to tolerate a solid diet, additional antiemetic requirements, additional analgesic requirements, and length of hospital stay were less in the metoclopramide group than in the control group, albeit without statistical significance. We found no adverse effects related to the use of metoclopramide (Table 3).

Discussion

Our study showed that, compared to placebo, intramuscular metoclopramide at 2 h after surgery promoted the recovery of gastrointestinal function by significantly shortening the time to first passage of flatus. The metoclopramide group was significantly faster (401.0 min) than the control group (1,785.3 ± 125.7 vs. 2,186.3 ± 103.9 min). About one-third (32%) of women in the metoclopramide group experienced first passage of flatus within 24 hours after surgery compared to only 4% of women in the control group. The average time to first passage of flatus in the metoclopramide group was 13.5 h faster than in the control group, supporting the hypothesis that metoclopramide is effective in preventing POI.

Notwithstanding, the results of our study indicated a longer time to first passage of flatus compared to that reported by Agah et al[11] (viz., 1,098.2 min), which might be explained by the different types of surgery and anesthesia. Our study used a total transabdominal hysterectomy under general anesthesia, while Agah et al[10] used cesarean section, with most patients receiving regional anesthesia. The type of surgical procedure and anesthesia have a significant impact on the recovery of the gastrointestinal system. The procedure of cesarean is less associated with direct bowel manipulation than hysterectomy. Surgical procedures require more bowel manipulation, which induces the inflammatory process, the main mechanism of POI[1]. In 2016, a Cochrane review[12] showed the benefit of epidural analgesia added to general anesthesia in abdominal surgery, accelerating the return of flatus and bowel movement faster than systemic opioid-based regimens plus general anesthesia. In addition, the regional analgesic technique decreased opioid consumption, lessening the impact on gastrointestinal motility.

A meta-analysis[8] of five clinical trials showed the beneficial effect of metoclopramide on ileus symptoms, as in our study that showed a reduction in POI symptoms after benign gynecologic surgery, especially postoperative gastrointestinal intolerance (POGI). Metoclopramide is widesly used as an antiemetic and effective in reducing postoperative nausea and/or vomiting[7] which is one of POI symptoms. Thus, postoperative metoclopramide injection decreased time to first passage of flatus and reduced ileus symptoms by enhancing bowel function. We assume that such a positive outcome might also increase patient satisfaction and reduce the costs of medical care.

Our results showed that time to first defecation, time to tolerate a solid diet, additional antiemetic requirements, additional analgesic requirements, and length of hospital stay trended to be less in the metoclopramide group than in the control group, albeit not statistically significant. These results differ from those of a meta-analysis[8] and Agah et al[11], who reported that metoclopramide significantly addressed these issues, perhaps explained by differences in types of operation and time to a step diet. Our study confirmed no adverse effects of metoclopramide as reported in the meta-analysis[9] vis-à-vis preventing POI.

The study's strengths included that it was a prospective, double-blind RCT design with an adequate sample size and used the I-FEED scoring

system to categorize POI symptoms. Limitations included (a) the use of a subjective measure of time to first passage flatus, which is a clinical parameter requiring patient self-observation for evaluating restoration of bowel function, and (b) the patients received food according to the hospital meal schedule regardless of the time duration after surgery, which might affect the evaluation of time to first defecation and time to tolerate a solid diet.

Conclusion

In summary, compared with placebo, postoperative intramuscular metoclopramide significantly enhanced the recovery of bowel function after benign gynecologic surgery and decreased the development of POI.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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