Original paper

Does elevated intra-abdominal pressure during laparoscopic colorectal surgery cause acute gastrointestinal injury?

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Abstract

Introduction: The incidence of acute gastrointestinal injury (AGI) after colorectal surgery is low when laparoscopic techniques are used. While elevated intra-abdominal pressure (IAP) and intra-abdominal hypertension (IAH) are associated with AGI grade II, little is known about the relation between increased IAP during laparoscopy and subsequent AGI.
Aim: To assess the impact of increased IAP during laparoscopic colorectal surgery on the incidence of postoperative AGI.
Material and methods: Sixty-six patients (41 men and 25 women) with colorectal cancer undergoing elective laparoscopic colorectal surgery were randomized into 3 groups, according to different IAP levels during CO_2 pneumoperitoneum (10 mm Hg, 12 mm Hg and 15 mm Hg). We recorded the incidence of AGI after surgery by assessing the following parameters: time to first flatus/defecation, time to first bowel movement, time to tolerance of semi-liquid food and the occurrence of vomiting/diarrhea. Moreover, inflammatory mediators were measured before the induction of CO_2 pneumoperitoneum and on postoperative day 1.
Results: Acute gastrointestinal injury occurred in 15 (27.3%) patients. In all 3 study groups, the elevation of IAP during CO_2 pneumoperitoneum did not significantly increase the occurrence of symptoms of AGI, vomiting or diarrhea. Lower IAP levels did not significantly accelerate recovery of gastrointestinal function or shorten postoperative hospital stay. The changes in serum IL-6 after surgery did not correlate with the value of IAP.
Conclusions: The level of IAP elevation during laparoscopic colorectal surgery does not increase the occurrence of AGI after surgery.

Key words: laparoscopic surgery, intra-abdominal pressure, colorectal carcinoma, acute gastrointestinal injury, postoperative recovery, inflammatory mediators.

Introduction

Acute gastrointestinal injury (AGI) was proposed by the Working Group on Abdominal Problems (WGAP) of the European Society of Intensive Care Medicine (ESICM) in 2012 [1]. According to the severity, a grading system of AGI was established for clinical and research purposes [1]. Similar symptoms of gastrointestinal dysfunction, including ileus, diar-

rhea and vomiting, can be observed in postoperative patients after abdominal surgery [2]. These symptoms are AGI grade I according to the ESICM WGAP recommendations [1].

Though technical improvements of laparoscopic colorectal surgery and perioperative care in recent years [3–5] have significantly reduced the incidence of AGI correlated symptoms, resulting in improved clinical recovery after colorectal surgery [6–8], con-

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tinuous insufflation of CO_2 into the peritoneal cavity still results in elevated intra-abdominal pressure (IAP) for several hours during surgery. Traditionally insufflation pressures are limited to an IAP of 15 mm Hg and are generally between 12 and 15 mm Hg, corresponding with intra-abdominal hypertension (IAH) grade I [9]. Furthermore, this level of IAH has been associated with AGI grade II, which means gastro-intestinal dysfunction more severe than might be expected in relation to standard abdominal procedures and surgery [1]. Moreover, in analogy to other intra-abdominal organs (like the liver, kidneys and spleen), the gut also suffers from a reduction of blood flow during IAH. A splanchnic ischemia-reperfusion (IR) injury is induced by the insufflation and desufflation of CO_2 pneumoperitoneum while IAP increases up to 12 mm Hg [10, 11], with postoperative AGI correlated symptoms observed in animal models of IR injury [12].

Most clinical trials on this regard has not examined the IAP level during CO_2 pneumoperitoneum. Moreover, Kronberg et al. did not introduce IAP into their novel predictive score evaluating possible risk factors for postoperative ileus (POI) after laparoscopic colorectal surgery [13]. Kozlik et al. had indicated the development of oxidative stress performed at high pressure pneumoperitoneum in a clinical study, but they focused mainly on the duration of laparoscopy, not on the intra-abdominal pressure [14]. Therefore, it remained to be discussed whether the level of IAP during laparoscopic surgery was related to the incidence of postoperative AGI. If this is the case, then the IAP induced by CO_2 pneumoperitoneum during laparoscopic surgery should be set below a critical threshold in the future.

In addition, POI, a common symptom of AGI, is considered to be a major determining factor related to increased hospital stay and increased recovery time after surgery [15, 16]. Various pathogenic mechanisms have been suggested in relation to POI, including inflammatory mediators such as interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α) [17]. These cytokine levels have been reported to increase in patients with high IAP induced by CO_2 pneumoperitoneum during laparoscopic surgery, and IL-6 and TNF-α levels may be elevated for more than 1 day [18]. In this study we compared the degree of increase of these cytokines caused by different levels of IAP. We hypothesized that IAP levels and cytokine levels correlate with the incidence of POI.

Aim

The aim of the study was to assess the impact of increased IAP during laparoscopic CO_2 pneumoperitoneum on the incidence of postoperative AGI. To verify the safety of laparoscopic colorectal surgery performed with IAP up to 15 mm Hg.

Material and methods

Ethics

The Ethics Committee of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, approved the protocol of this study. The project was registered at the Chinese Clinical Trial Registry (Registration Number: ChiCTR-TRC-13003292) in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. Out of 84 consecutive patients who met the study inclusion criteria, 66 (78.6%) agreed to participate after signed informed consent was obtained.

Sample size calculation

The standardized formula $N = \pi_0(1 - \pi_0)(Z\alpha + Z\beta)^2/\delta^2$ was used to calculate the sample size ($\alpha = 0.05$, $1 - \beta = 0.2$, $Z\alpha = 1.6449$, $Z\beta = 1.2816$; π_0 refers to the population rate of endpoint; δ refers to the expected significant difference of sample rate). In a preliminary experiment before this study, we observed 13 eligible patients who met the inclusion criteria within 30 days. Five (38.5%) patients presented AGI correlated symptoms. On the other hand, a reduction of incidence of AGI by 50% was considered clinically significant. Thus, $\pi_0 = 38.5\%$, $\delta = \pi_0/2$. The theoretical sample size (N) hence is 54.76. With a loss to follow-up probability of about 0.2, the actual sample size was calculated at $(1 + 0.2) \times N = 65.71 \approx 66$ in this study.

Patients and eligibility

Patients from Shanghai Minimally Invasive Surgery Center, Shanghai, China were enrolled for this study. Inclusion criteria were as follows: age between 40 and 80 years; American Society of Anesthesiologists (ASA) score I or II; a biopsy proven histological diagnosis of colorectal carcinoma; no clinical evidence of metastasis; undergoing laparoscopic colorectal surgery. Exclusion criteria were: contraindication of laparoscopic surgery (e.g. extensive intra-abdominal adhesion); emergency procedure; evidence of bowel ileus/obstruction before

surgery; unresectable mass; a planned stoma (e.g. abdominoperineal resection of rectal carcinoma, protective ileal stoma); an unexpected stoma; conversion to open surgery; short-term re-operation; postoperative opioid analgesic usage; or persistent uncorrected severe fluid and electrolyte imbalance (e.g. hypokalemia, hypomagnesemia) [19].

Study design and intervention

The eligible patients were randomized into 3 groups using Microsoft Excel software (Redmond, WA, USA), in which the IAP of CO_2 pneumoperitoneum during laparoscopic surgery was set at three levels in different groups: group 1: 10 mm Hg; group 2: 12 mm Hg; and group 3: 15 mm Hg. The fixed IAP was set and monitored via the CO_2 pneumoperitoneum insufflation system (STORZ Thermoflator, KARL STORZ GmbH & Co. KG, Tuttlingen, Germany) by an anesthesiologist.

The laparoscopic procedures were standardized and performed by an identical surgical team in all groups. Right hemicolectomy was performed in a supine position with the head of the bed raised 30°, while sigmoid colectomy and anterior resection of the rectum were performed in a modified lithotomy position (head-down tilt). Left hemicolectomy required an alteration between these two positions. A small incision with a varying size corresponding to the resection specimen was performed in order to accomplish the anastomosis. The nasogastric tube (NG tube) was inserted before the anesthesia induction and was removed immediately when the patients regained consciousness in order to avoid anesthetic accidents (inhalation of vomit).

Blinding

A double-blind method was adopted in this study. Patients, operating surgeon or surgeons taking care of patients were not informed about the IAP level applied during the surgery; only the anesthesiologist was aware, keeping the IAP level fixed during laparoscopy.

End-points and outcomes

The first flatus/defecation, the first bowel movement (the sense of bowel sound before flatus/defecation) and the occurrence of vomiting/diarrhea were self-reported by the patient and recorded in the study files. Patients were visited at least once daily after surgery by an experienced surgeon evaluating clinical recovery, including the tolerance of semi-liquid food, other postoperative intra-abdominal complications such as anastomotic leak, surgical site oozing, etc, and finally the discharge time. The anesthesiologist recorded the duration of surgery and CO_2 pneumoperitoneum and the intra-operative blood loss. At the onset of the CO_2 pneumoperitoneum and at 6 a.m. on postoperative day 1 (POD1), serum IL-6 and TNF-α levels were measured.

Criteria for allowing semi-liquid food were: normothermia; no adverse reactions with liquid food; normal defecation/free-flow of stoma. Discharge criteria included: tolerance of semi-liquid food for more than 24 h; normothermia; normal defecation/free-flow of stoma.

Postoperative ileus was defined as absence of flatus/defecation or bowel movement before POD2 according to Vather *et al.* [2]. The AGI was considered to occur in patients who presented: nausea/vomiting unrelated to anesthetic reaction; diarrhea (three or more loose or liquid stools per day) for more than 1 day; POI.

Statistical analysis

The data collection was done using EpiData 3.1 software (freeware available at www.epidata.dk, Odense, Denmark), while all statistical analysis was performed with the IBM Statistical Package for the Social Sciences (SPSS 13.0, Chicago, IL, USA). Continuous data were expressed by mean ± SD, and intergroup differences were determined by one-way analysis of variance (ANOVA) analyses (represented as $\bar{x} \pm s$). Categorical data were expressed as frequency distributions and/or percentages, and the χ^2 test or Fisher's exact test was used to determine intergroup differences. For other variables, a non-parametric test was used (represented as median and quartiles). Two-sided *p* values < 0.05 were considered to indicate statistical significance.

Results

Patient demographics

All 66 enrolled patients were analyzed, and each group consisted of randomly assigned 22 patients. No statistically significant differences in baseline characteristics were noted between patients in the 3 groups (Table I). Tumor location, type of surgery, duration of surgery, duration of CO_2 pneumoperito-

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Table I. Patient demographics and characteristics (all patients enrolled)

Baseline characteristic	Group 1 (IAP = 10 mm Hg) n = 22	Group 2 (IAP = 12 mm Hg) n = 22	Group 3 (IAP = 15 mm Hg) n = 22	Value of p
Age ($\overline{x} \pm s$)	61.9 ±8.7	64.3 ±11.7	64.7 ±6.4	0.476[#]
Gender ratio (male/female)	14/8	13/9	14/8	0.938[*]
Tumor location, n (%):				0.146[‡]
Ascending colon	2 (9.1)	6 (27.3)	7 (31.8)	
Transverse colon	0 (0)	3 (13.6)	0 (0)	
Descending colon	1 (4.5)	1 (4.5)	1 (4.5)	
Sigmoid colon	11 (50)	7 (31.8)	11 (50)	
Rectum	8 (36.4)	5 (22.7)	3 (13.6)	
Type of surgery, n (%):				0.088[‡]
Right hemicolectomy	2 (9.1)	9 (40.9)	7 (31.8)	
Left hemicolectomy	2 (9.1)	1 (4.5)	1 (4.5)	
Sigmoid colectomy	0 (0)	0 (0)	3 (13.6)	
Anterior resection of rectum	15 (68.2)	11 (50)	9 (40.9)	
Stoma or subtotal colectomy	3 (13.6)	1 (4.5)	2 (9.1)	
Operation time [h]:				0.453[§]
Median (quartile)	1.6 (1.4–2.0)	1.8 (1.6–2.2)	1.9 (1.5–2.2)	
Pneumoperitoneum time [h]:				0.185[§]
Median (quartile)	0.9 (0.8–1.1)	1.1 (0.9–1.3)	1.0 (0.8–1.3)	
Intra-operative blood loss [ml]:				0.562[§]
Median (quartile)	100 (50–163)	80 (50–120)	100 (50–100)	
Removal of NG tube within 6 h after surgery, n (%)	22 (100)	21 (95.5)	18 (81.8)	0.117[‡]
AJCC staging, n (%):				0.437[‡]
I	7 (31.8)	5 (22.7)	9 (40.9)	
II	6 (27.3)	8 (36.4)	5 (22.7)	
III	8 (36.4)	4 (18.2)	6 (27.3)	
IV	1 (4.5)	5 (22.7)	2 (9.1)	
Postoperative intra-abdominal complications:				0.171[‡]
None	22 (100)	21 (95.5)	19 (86.4)	
Chylous fistula	0	1 (4.5)	0	
Anastomotic leak	0	0	1 (4.5)	

[#]*Analysis of variance (ANOVA) test – Welsh's test, *Pearson's χ^2 test, [‡]χ^2 test – Fisher's exact test, [§]nonparametric test – Kruskal Wallis' test.*

neum, intra-operative blood loss, and removal of NG tube within 6 h after surgery were not significantly different between the 3 groups (Table I). The postoperative anatomopathologic staging (based on the TNM classification system, 2010, 7th edition) was also not statistically significantly different ($p = 0.44$). The length of follow-up ranged from 7 to 14 days after surgery and 4 (6.1%) patients presented with early postoperative intra-abdominal complications other than AGI: one chylous fistula, one anastomotic leak and two cases of surgical site oozing. However, we could not determine a statistical correlation between IAP and early postoperative intra-abdominal complications other than AGI ($p = 0.17$).

Postoperative AGI incidence

Of the 66 enrolled patients, 11 patients were excluded from the AGI analysis (respectively 3, 3 and 5 in groups 1, 2 and 3). The reasons for exclusion were as follows: 4 patients underwent an unexpected stoma; the other 6 received opioid analgesia after surgery; and finally in 1 patient from group 1, the surgeon changed the IAP level (from 10 to 15 mm Hg) during surgery.

Of the 55 remaining patients, 15 (27.3%) patients presented with postoperative AGI correlative symptoms (respectively 6, 3 and 6 in groups 1, 2 and 3), of which 8 cases were regarded as AGI grade I and 7 cases were classified as AGI grade II. Neither the incidence nor the grade of AGI showed a statistically significant difference between the 3 groups ($p = 0.41$, and $p = 0.36$ respectively). Recovery of gastrointestinal function was not significantly improved in patients receiving a low IAP level (group 1) compared with those having received higher IAP levels (groups 2 and 3) during laparoscopy. The level of IAP elevation was not related to increased occurrence of AGI symptoms, neither POI ($p = 0.92$) nor diarrhea ($p = 0.67$). Postoperative hospital stay was similar in the 3 groups ($p = 0.27$) (Table II).

Compared with the 55 patients included in the AGI analysis, the use of opioid analgesia and the application of the stoma did not alter the time to the first flatus/defecation, the time to the first bowel movement or the post-operative hospital stay (Table III). However, patients with a protective ileal stoma achieved earlier tolerance of semi-liquid food than others ($p < 0.001$, Mann-Whitney U-test).

Serum cytokine levels

The patients in the 3 groups had equal serum IL-6 and TNF-α levels at the onset of CO_2 pneumoperitoneum (Table IV). At 6 a.m. on POD 1, serum IL-6 levels were increased ($p < 0.001$, Wilcoxon's test) while TNF-α levels remained virtually unchanged compared to the pre-operative levels ($p = 0.17$, Wilcoxon's test). However, the increase in IL-6 levels was not significantly different in the 3 groups ($p = 0.27$) (Table IV). The 11 POI cases did not have a significantly increase in IL-6 levels compared to other patients ($p = 0.98$, Mann-Whitney U-test).

Discussion

For the past 20 years, CO_2 pneumoperitoneum during laparoscopic surgery has been considered to compromise cardiopulmonary functions due to the increased IAP during the procedure [20]. Hemodynamic changes such as a decrease in cardiac index, an increase in mean arterial blood pressure (MAP), systemic vascular resistance (SVR) and central venous pressure (CVP) have been observed previously, while alterations in respiratory function include reduced compliance and a transient reduction in lung volumes and capacities [20–22]. Increased IAP may result in neuroendocrine alterations with an increase in plasma concentration of renin, aldosterone, cortisol, adrenalin and noradrenalin in various degrees [20–22].

However, little is known about acute gastrointestinal dysfunction caused by CO_2 pneumoperitoneum during laparoscopic surgery. Possible reasons include the variety of definitions and classification of GI dysfunction [23], the lack of reliable biomarkers for assessing GI function [24], and the underestimated GI injury in post-laparoscopic patients [25, 26].

The consensus and recommendations about acute gastrointestinal injury (AGI) [1] allowed us to investigate these issues. The gastrointestinal symptoms of AGI, including nausea/vomiting [27], diarrhea (three or more loose or liquid stools per day) [28, 29], paralysis of the lower GI tract (paralytic ileus) [15], and abnormal bowel sound [30] can be observed frequently in post-operative patients undergoing laparoscopic colorectal surgery. Thus far, there has been no published study indicating whether the elevated IAP during laparoscopic surgery (generally between 12 and 15 mm Hg) is associated with postoperative AGI or is related to increased occurrence of the above-mentioned GI symptoms.

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Table II. The AGI correlated parameters (only valid patients included)

AGI parameters	Group 1 $n = 19$	Group 2 $n = 19$	Group 3 $n = 17$	Value of p
AGI incidence, n (%):	6 (31.6)	3 (15.8)	6 (35.3)	0.413[‡]
AGI grade, n (%):				0.361[§]
None	13 (68.4)	16 (84.2)	11 (65.7)	
Grade I	2 (10.5)	2 (10.5)	4 (23.5)	
Grade II	4 (21.1)	1 (5.3)	2 (11.8)	
POI incidence, n (%):	4 (21.1)	3 (15.8)	4 (23.5)	0.915[‡]
Time to first bowel movement [h]:				0.209[#]
Average ± SD ($\overline{x} \pm s$)	36.9 ±24.6	25.9 ±16.4	32.9 ±12.3	
Time to first flatus/defecation [h]:				0.545[§]
Median (quartile)	31.3 (16.8–45.6)	40.8 (20.9–64.5)	31.9 (20.8–51.0)	
Time to semi-liquid food [h]:				0.531[§]
Median (quartile)	142.3 (118.9–144.9)	137.4 (118.7–143.4)	139.5 (119.1–145.5)	
Days with vomiting, n (%):				1.000[§]
0	18 (94.7)	18 (94.7)	16 (94.1)	
1	1 (5.3)	1 (5.3)	1 (5.9)	
Days with diarrhea, n (%):				0.670[§]
0	14 (73.7)	16 (84.2)	13 (76.5)	
1	4 (21.1)	3 (15.8)	3 (17.6)	
2	0	0	1 (5.9)	
3 or more	1 (5.3)	0	0	
Post-operative hospital stay [days]:				0.638[§]
Median (quartile)	8 (8–9)	8 (8–9)	8 (8–9.5)	

[#]*Analysis of variance (ANOVA) test – Welsh's test,* [‡]*χ^2 test – Fisher's exact test,* [§]*Nonparametric test – Kruskal-Wallis test.*

Our present prospective randomized controlled study indicates no significant correlation between the level of elevated intra-abdominal pressure during surgery and the incidence of postoperative AGI. Out of the total 66 enrolled patients, 11 (16.7%) were excluded from the AGI analysis in accordance with the exclusion criteria, which corresponded to the loss to follow-up probability of about 20%. The incidence of AGI was 35.3% in group 3 (IAP = 15 mm Hg), similar to the result of the preliminary experiment (38.5%). The standard deviation (SD) of the other end-points in this study was 18.9 h (time to the first bowel movement), 21.6 h (time to the first flatus/defection) and 18.8 h (time to tolerance of semi-liquid food) respectively, which was in line with the results of Muller *et al.* [31].

The strengths of the present study are as follows. First, a blinded surgeon was appointed to visit the patients after surgery and to decide the discharge time, limiting bias. The operating surgeon was also blinded with regard to the level of IAP applied during laparoscopy to avoid bias. Second, the serum inflammatory mediators were measured with the same testing method and the same lab machine. Third, in order to avoid a confounding bias, opioid analgesia was avoided if other analgesics were sufficiently effective (protocol for postoperative analgesics: level I: paracetamol; level II: nefopam, phloroglucinol; level III:

Table III. Analysis of excluded patients

Parameters	Valid patients n = 55	Opioid analgesia n = 4	Stoma n = 6	Value of p
Time until bowel movement [h]:				0.652*
Average ± SD ($\overline{x}$ ± s)	31.9 ±18.9	34.1 ±22.0	23.4 ±10.5	
Time until flatus/defecation [h]:				0.256*
Average ± SD ($\overline{x}$ ± s)	36.8 ±21.6	46.0 ±18.3	23.4 ±10.5	
Time until semi-liquid food [h]:				0.004§
Median (quartile)	138.8 (118.9–144.3)	130.3 (111.8–144.6)	81.3 (67.4–92.6)	
Post-operative hospital stay [days]:				0.638§
Median (quartile)	8 (8–9)	8.5 (8–9)	8 (8–8.5)	

Analysis of variance (ANOVA) test, §nonparametric test – Kruskal-Wallis test.

Table IV. Serum cytokine levels (only valid patients included)

Cytokine	Group 1 n = 19	Group 2 n = 19	Group 3 n = 17	Value of p
Pre-operative IL-6 [ng/l]:				0.080§
Median (quartile)	2.0 (2.0–2.7)	2.8 (2.0–5.9)	2.1 (2.0–3.0)	
Post-operative IL-6 [ng/l]:				0.808§
Median (quartile)	10.7 (7.5–17.7)	11.3 (5.4–14.5)	9.4 (6.7–18.2)	
Pre-operative TNF [ng/l]:				0.185§
Median (quartile)	9.5 (7.4–10.7)	9.4 (8.5–13.4)	8.5 (7.8–9.5)	
Post-operative TNF [ng/l]:				0.272§
Median (quartile)	9.0 (8.5–12.5)	10.3 (7.8–12.0)	8.2 (6.4–12.2)	
Delta IL-6 [ng/l]:				0.266§
Median (quartile)	8.0 (5.0–14.0)	7.0 (1.8–10.3)	7.4 (4.7–15.0)	

§Nonparametric test – Kruskal-Wallis test.

tramadol or subcutaneous morphine). Fourth, fluid and electrolyte imbalances were adjusted as soon as possible, especially hypokalemia and hypomagnesemia, as these have been reported to aggravate bowel ileus [18]. Finally, other confounding factors such as the duration of surgery and the duration of CO_2 pneumoperitoneum were similar among the three groups.

The limitations of our study are as follows: First, the lack of objective serum biomarkers for GI function/dysfunction does not permit a quantitative integrative analysis. We could only compare the occurrence and recovery of GI symptoms separately. Second, the incidence of AGI in our study was low, so that statistically significant differences may not be detected due to a small sample size and possibly low statistical power. Third, although some possible confounding factors, such as type of surgery, duration of surgery and CO_2 pneumoperitoneum, and removal of the NG tube within 6 h after surgery, were equally balanced between the three study groups, the results could have been more convincing if we had done a stratified analysis on these factors in a larger sample size. Fourth, the IAP was not measured postoperatively, to check whether a postoperative IAP increase was related to AGI.

With regard to inflammatory mediators that play a role in POI, such as IL-6 and TNF-α [17, 32], previous studies have reported increased serum levels after laparoscopic surgery [18, 33–35]. The elevated

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IAP in this study did not attenuate the immune response, but the test frequency was restricted. Previous studies have shown a dose-response effect in relation to IAP elevation and serum cytokine levels. Hence dynamic monitoring of these cytokines would have provided more information reflecting the real postoperative immune status.

Conclusions

The incidence of postoperative AGI in patients undergoing laparoscopic colorectal surgery is not correlated with the level of elevated intra-abdominal pressure during CO_2 pneumoperitoneum. These "negative" results need to be validated in a multi-centre randomized controlled trial with a larger sample size.

Conflict of interest

The authors declare no conflict of interest.

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