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ORIGINAL INVESTIGATION

Fluid administration in cytoreductive surgery with hyperthermic intraperitoneal chemotherapy: neither too much nor too little

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Abstract

Introduction: Intraoperative fluid therapy in cytoreductive surgery with hyperthermic intraperitoneal chemotherapy plays an important role in postoperative morbidity. Studies have found an association between overload fluid therapy and increased postoperative complications, advising restrictive intraoperative fluid therapy. Our objective in this study was to compare the morbidity associated with restrictive versus non-restrictive intraoperative fluid therapy.

Methods: Retrospective analysis of a database collected prospectively in the Anesthesiology Service of Virgen del Rocío Hospital, from December 2016 to April 2019. One hundred and six patients who underwent complete cytoreductive surgery and hyperthermic intraperitoneal chemotherapy were divided into two cohorts according to Fluid Therapy received 1. Restrictive ≤ 9 mL.kg^{-1}.h^{-1} (34 patients), 2. Non-restrictive ≥ 9 mL.kg^{-1}.h^{-1} (72 patients). Percentage of major complications (Clavien-Dindo grade III–IV) and length hospital stay were the main outcomes variables.

Results: Of the 106 enrolled patients, 68.9% were women; 46.2% had ovarian cancer, 35.84% colorectal cancer, and 7.5% peritoneal cancer. The average fluid administration rate was 11 ± 3.58 mL.kg^{-1}.h^{-1}. The restrictive group suffered a significantly higher percentage of Clavien-Dindo grade III–IV complications (35.29%) compared with the non-restrictive group (15.27%) ($p = 0.02$). The relative risk associated with restrictive therapy was 1.968 (95% confidence interval: 1.158–3.346). We also found a significant difference for hospital length of stay, 20.91 days in the restrictive group vs 16.19 days in the non-restrictive group ($p = 0.038$).

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Conclusions: Intraoperative fluid therapy restriction below 9 mL.kg^{-1}.h^{-1} in cytoreductive surgery with hyperthermic intraperitoneal chemotherapy was associated with a higher percentage of major postoperative complications.

Introduction

Although its etiology is heterogeneous, peritoneal cytoreductive surgery (CRS) is considered as a pathological entity with characteristics and peculiarities common to all of them. This procedure is characterized by long periods of extreme surface exposure, which results in a significant loss of fluids and proteins, decreases intravascular volume, and is followed by perfusion with intraperitoneal chemotherapy (HIPEC) at 42 °C. The associated morbidity ranges from 35% to 50%.[1–3]

Intraoperative replacement of the lost volume seems a fundamental point in the management of these patients to ensure an intravascular volume that allows adequate tissue perfusion[1–5]; however, avoiding intraoperative fluid overload is important to avoid the increased morbidity confirmed in multiple studies.[6–10]

It is indisputable that this surgery requires advanced hemodynamic monitoring that guarantees adequate cardiac output and splanchnic perfusion.[3–5] Recently, goal-directed therapy has been advised, and the use of stroke volume variation (SVV) to guide fluid therapy has become widespread.[12–15]

However, although these hemodynamic parameters are the best indices to predict a patient's cardiac index response to fluid administration, these parameters have limitations and should not be confused with a patient's actual intravascular volume or preload. In addition, recent work questions the accuracy of SVV as a predictor of volume response during major abdominal surgery,[15] and other authors have questioned the suitability of ''preload dependence'' because of its consequences in the microcirculation.[16]

Our aim in this study was to compare the morbidity associated with restrictive versus non-restrictive intraoperative fluid therapy in patients undergoing CRS and HIPEC.

Methods

This was a two-cohort observational study performed in the Anesthesiology Service of the Virgen del Rocío University Hospital between December 2016 and April 2019. The study was approved by the center's ethics committee (Portal de Etica de la Investigación Biomédica de Andalucía, protocol number 1472-N-19; approval date 23 October 2019).

Adult patients diagnosed with primary or secondary peritoneal carcinomatosis who underwent scheduled CRS and HIPEC were included in this study. Patients in whom complete reduction of the tumor mass was not possible, patients younger than 18 years of age, procedures in which the duration of surgery and the fluid therapy administered were not reliably recorded, and severely clinically deteriorated patients admitted for surgery were excluded (Fig. 1).

We used paclitaxel for ovarian and peritoneal tumors, and mitomycin C for colorectal cancer, appendiceal tumors, and peritoneal pseudomyxoma using an open abdominal coliseum technique.

We collected patients' data for age, comorbidities, American Society of Anesthesiologists (ASA) physical status, peritoneal cancer index, tumor type, intervention time (hours), number of anastomoses, amount and type of fluid therapy (total volume and weight-adjusted volume in mL.kg^{-1}.h^{-1}), blood products, pre- and postoperative blood protein levels, length of stay in the intensive care unit, and length of hospital stay.

As variable outcomes, we recorded the major complications (grade III–IV) according to the Clavien-Dindo classification,[17] and length of hospital stay.

Clavien-Dindo is a classification of surgical complications in 5 degrees:

- Grade I: Any deviation from the normal postoperative.
- Grade II: Requiring pharmacological treatment with drugs other than such allowed for grade I complications (blood transfusions).
- Grade III: Requiring surgical, endoscopic, or radiological intervention.
- Grade IV: Life-threatening complication requiring critical care management.
- Grade V: Death of a patient.

In all patients, we performed combined anesthesia using a thoracic epidural and general anesthesia. We monitored patients' cardiac index using the FloTrac or VolumeView EV1000 (Edwards Lifesciences; Irvine, CA) systems. As maintenance fluid therapy, we used a balanced crystalloid (Plasma-Lyte®; Baxter Healthcare, Toongabbie, NSW, Australia) and as a colloid, we use hydroxyethyl-starch solutions, under the restrictions applied by European Medicines Agency, and 20% albumin.

We extubated 75.5% of the patients in the operating room and the remainder within a few hours, without difficulty. Only one patient required mechanical ventilation, for 48 hours, and 38.7% of patients required norepinephrine during the first hours postoperatively. The average stay in the intensive care unit was 2 days.

In the first 16 patients patients monitored with EV1000 (Edwards Lifesciences; Irvine, CA), we performed a total of 47 Transpulmonary Thermodilutions, and despite an average fluid administration of 11.5 mL.kg^{-1}.h^{-1} [9.5–13.76] during surgery, the patients presented at the end of the surgery, a lower Global End-Diastolic Volume Index (GEDI) than the initial, 531 [460–603] versus 562 [495–624] mL.m^{-2} (nor-

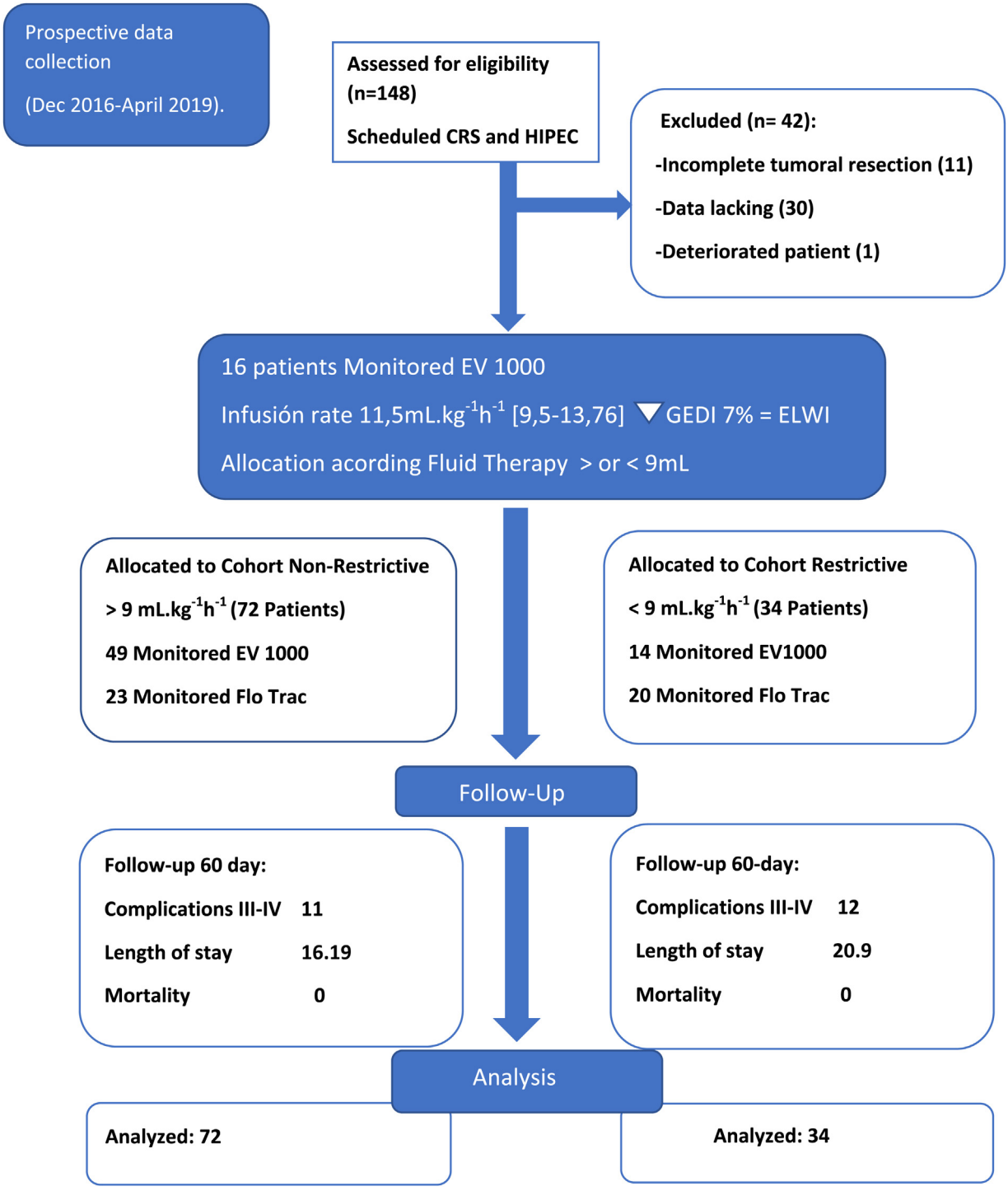

Figure 1 STROBE Flow Diagram.

mal value between 680–800 mL.m^{-2}). Using the indexed Extravascular Pulmonary Water (ELWI), we evaluated the passage of this fluid into the interstitial space and the possible repercussions of our fluid therapy on lung function, the mean of which remained unchanged at 8 mL·kg^{-1}. Therefore, we can conclude that therapy below 9 mL.kg^{-1}.h^{-1} is restrictive in most cases.

Regardless of the monitoring and endpoints used, we divided patients into two cohorts according to the fluid therapy: restrictive fluid therapy of < 9 mL.kg^{-1}.h^{-1} or non-restrictive fluid therapy of > 9 mL.kg^{-1}.h^{-1}.

Statistical analysis

Qualitative variables were expressed with absolute and relative frequencies. Quantitative variables were expressed with mean and standard deviation, and with median and

Table 1 Patients' characteristics.

	Non-restrictive therapy (n = 72)		Restrictive therapy (n = 34)	
	Percentage %	Count	Percentage %	Count
Sex				
Female	77.8%	56	50%	17
Male	22.2%	16	50%	17
ASA				
I	5.6%	4	8.8%	3
II	70.8%	51	52.9%	18
III	23.6%	17	38.2%	13
Diabetes Mellitus	13.9%	10	14.7%	5
Arterial hypertension	30.5%	22	23.52%	8
COPD	5.5%	4	2.9%	1
Primary tumor				
Ovary	52.7%	38	32.3%	11
Colorectal	29.2%	21	50%	17
Peritoneal	6.9%	5	8.8%	3
Pseudomyxoma	4.2%	3	5.9%	2
Appendix	4.2%	3	2.9%	1
	Mean	SD	Mean	SD
Age	57.06	10.65	57.24	11.43
Weight	64.04	11.08	77	14.05
BMI	23.11	6.32	27.23	4.04
PCI	23.22	8.17	17.25	10.08

ASA, American Society of Anesthesiologists physical status; BMI, body mass index; COPD, chronic obstructive pulmonary disease; PCI, peritoneal cancer index.
Qualitative variables were expressed with absolute and relative frequencies Quantitative variables are expressed as Mean and SD (Standard Deviation).

interquartile range, if the distribution was not normal. The χ^2 test was used for qualitative variables, or Fisher's exact test, if necessary, and we used Student's *t*-test or analysis of variance for quantitative variables.

Differences between the groups were statistically significant at $p < 0.05$ or if the 95% confidence interval of the odds ratio excluded a value of 1. The data were processed and analyzed using the SPSS v 24.0 (IBM Corp., Armonk, NY) statistical package.

Results

We enrolled 106 patients undergoing cytoreductive surgery and HIPEC; 46.22% were diagnosed with ovarian cancer, 35.84% with colorectal cancer, 7.5% with peritoneal cancer, 4.7% with peritoneal pseudomyxoma, 3.77% with appendicular cancer, and 1.97% with other cancers. The general characteristics of our patients are shown in Table 1.

The average fluid administration rate, or the mean rate of intraoperative fluid therapy administered was 11 $\pm$ 3.58 $mL.kg^{-1}.h^{-1}$ When we analyzed data for all patients, we found marked variability in data for patients with weights at extreme values; patients weighing < 50 kg (n = 4) received a mean of 16.24 $\pm$ 1.7 $mL.kg^{-1}.h^{-1}$, while patients weighing > 85 kg (n = 12) received a mean of 8.4 $\pm$ 2.44 $mL.kg^{-1}.h^{-1}$, suggesting that anesthesiologists were not always aware that excess or insufficient fluid volumes were being administered.

Table 2 Characteristics of the patients in each group.

Parameters	Non-restrictive therapy (n = 72)	Restrictive therapy (n = 34)	*p*-value
ASA	2.18	2.29	0.325
Age	57.06	57.24	0.937
Anastomoses	0.82	0.79	0.871
PCI	23.22	17.2	0.006
Surgery hours	10.19	9.76	0.216
Packed red blood cells	0.43	0.18	0.101
Basal protein	7.26	8.96	0.208
Final protein	4.39	4.85	0.002
Relation albumin/Crystalloid (g/L)	5.62	4.10	0.22
Length of stay (days)	16.19	20.91	0.038

ASA, American Society of Anesthesiologists; PCI, peritoneal cancer index.
All data are expressed as mean.

In contrast, the fluid volume distribution in patients with average weight was more random. The body mass index of our patients was in the normal range, and similar in both groups.

The means in each group were similar for ASA physical status, age, number of anastomoses, and duration of the intervention. We found a significant difference only regard-

Table 3 Intraoperative fluid therapy.

Fluid therapy	Average total n = 106	Restrictive n = 34	Non-restrictive n = 72
mL.kg^{-1}. h^{-1} Total	11 ± 3.5	7.13 ± 1.4	12.82 ± 2.7
mL.kg^{-1}.h^{-1} Crystalloids	10.46 ± 3.4	6.68 ± 1.3	12.24 ± 2.6
Colloids mL.kg^{-1}.h^{-1}	0.54 ± 0.6	0.44 ± 0.6	0.59 ± 0.5
HES 6% mL.kg^{-1}.h^{-1}	0.22 ± 0.6	0.22 ± 0.6	0.24 ± 0.5
HES 6% mL	158.82 ± 360	183.8 ± 344	145.83 ± 369
Albumin g	43.68 ± 42.3	28 ± 31.0	50 ± 45.2
Relation g Alb/L Crist.	5.15 ± 5.2	4.10 ± 5.5	5.62 ± 5
Packed red blood cells	0.35 ± 0.74	0.18 ± 0.57	0.43 ± 0.80
Basal hemoglobin	12.31 ± 1.62	12.35 ± 1.35	12.30 ± 1.75
Final hemoglobin	11.05 ± 1.86	11.56 ± 2.08	10.82 ± 1.72
Basal creatinine	0.74 ± 0.20	0.77 ± 0.17	0.72 ± 0.21
Final creatinine	0.71 ± 0.21	0.75 ± 0.19	0.70 ± 0.22

HES, hetastarch.
All data are expressed as mean (standard deviation).

Table 4 Clavien-Dindo complications.

Clavien-Dindo complications	Restrictive (n = 34)	Non-restrictive (n = 72)	p-value
Grade I–II. Minor complications (%)	**(9/34) 26.5**	**(18/72) 25**	**p = 0.10**
-Postoperative ileus	2	3	
-Urinary infection	1	2	
-Transfusion red blood cells	1	8	
-Pleural effusion	0	1	
-AKI (Acute Kidney Injury)	5	4	p = 0.11
Grado III–IV. Major complications (%)	**(12/34) 35.3**	**(11/72) 15.3**	**p = 0.02**
Complication III	**6**	**7**	
-3a. Intraabdominal abcess (percutaneous drainage)	3	4	
-3b. Reoperation under general anaesthesia	3	3	
Complication IV (Re-admission ICU)	**6**	**4**	
-Pulmonary oedema	0	1	
-Septic shock	2	1	
-Anastomotic leakage	4	2	
Length of stay:			
-Mean	20.91	16.19	p = 0.038
-Median	18 [11.5–24.5]	13.5 [11–18.75]	p = 0.058
60-day mortality	0	0	

ICU, intensive care unit.
Complications count and proportion. Length of stay expressed as day.

ing the higher rate of peritoneal cancer in the group that received non-restrictive fluid therapy, and for postoperative blood protein levels, which were higher in the restrictive therapy group, as shown in Table 2.

Patients who received restrictive fluid therapy at a mean rate of 7.13 ± 1.43 mL.kg^{-1}.h^{-1} suffered a higher percentage (12 of 34 patients in restrictive group; 35.29%) of Clavien-Dindo grade III and IV complications compared with the non-restrictive therapy group, who received fluids at a mean rate of 12.45 ± 2.66 mL.kg^{-1}.h^{-1}, with a percentage of serious complications of 15.27% (11/72 patients) (Chi-square; p = 0.02). There were no mortalities at 60 days.

Table 3 shows the amount of crystalloid, colloid, and albumin that patients received. Although the median hospital length of stay in the 106 patients was 14.4 days (IQR, 11–21), we also found a longer length of stay for the patients receiving restrictive therapy, with an average of 20.91 days compared with 16.19 days in the non-restrictive therapy group (p = 0.02).

The different postoperative complications and the length of stay are shown in Table 4. The risk estimate for restrictive therapy was 1.968 (95% confidence interval: 1.158–3.346).

Discussion

Cytoreductive surgery and HIPEC involve much higher fluid losses compared with other abdominal surgeries because of the extensive resection surface and the prolonged duration (mean: 8–10 h).[3,6,18] It is of great importance to individualize the cut-off point regarding restricted or non-restrictive

therapy in this type of procedure, and to set an intraoperative fluid perfusion rate adjusted to the patient's weight and procedure duration to avoid unintended overload or deficit volumes associated with the most extreme weight values.

As a solution, goal-guided therapy has been recommended, which maintains a restrictive basal rate and guides the added bolus-shaped fluid therapy in response to increased SVV or pulse pressure variation (PPV).[11–15]

However, dynamic parameters, as the name suggests, change frequently during the different phases of surgery, and increasing a patient's cardiac index depends on preload as well as contractility, heart rate, and systemic vascular resistance. This is consistent with findings in the OPTIMISE trial[15] in which the precision of the predictive powers of SVV and PPV was insufficient to recommend their perioperative use in major abdominal surgery.

Furthermore, HIPEC involves a high intra-abdominal pressure of up 10–14 mmHg,[18,19] which also affects the predictive power of SVV and PPV. Díaz et al.,[20] in a study performed in pigs, described the loss of correlation between the increase in SVV and PPV and the response of the cardiac index to a fluid bolus after inducing intra-abdominal hypertension.

Moreover, a recent publication questioned the suitability of ''preload dependence'' because of the damage to the microvascular perfusion that this procedure produces.[16] This fact has been proven in sublingual circulation, which was highly correlated with gut and renal microcirculation in several studies.[21–23] These factors could explain our finding that a significant increase in major complications occurred in patients who received restrictive therapy, and a literature review revealed similar results.

Holte et al.,[6] conducted a randomized controlled double-blind trial comparing restrictive and liberal perioperative fluid therapy in 32 patients undergoing colonic surgery. Although the study was designed to detect changes in Pulmonary function, also found an increase in total complications in the restrictive therapy group vs the liberal therapy group: 18 vs. 1, respectively ($p < 0.01$). Six of 16 patients in the restrictive group (37.5%) suffered Clavien-Dindo grade III–IV complications compared with only one patient (6.25%) in the liberal fluid therapy group. The study also showed a significantly longer length of stay in the restrictive fluid therapy group vs the liberal fluid therapy group of 4 vs. 2.5 days, respectively ($p = 0.03$).

CRS is associated with an enormous loss of proteins and albumin,[3] which cause a fall in oncotic pressure and an increase in capillary permeability that we must try to mitigate. Some randomized clinical trials demonstrated a benefit with goal-guided therapy and showed a greater benefit with colloids compared with crystalloids,[12] but without confirming whether the benefit was secondary to significant restriction or a greater proportion of colloids to preserve osmotic pressure intraoperatively with marked protein loss.

It is difficult to reach consensus on the volume of fluid replacement if we use completely different solutions,[24] with different proportions of colloids/crystalloids or grams of albumin/L of crystalloid. Unlike previous studies, in our work, the proportion of colloids and albumin was similar in both groups.

Regarding crystalloids, in our study, we used a buffered crystalloid such as Plasma-Lyte®, which maintains a better acid–base balance during surgery compared with 0.9% saline. A 0,9% saline causes more metabolic disorders such as saline overload and hyperchloremic acidosis[25] and must be avoided as an intraoperative fluid.[26] Furthermore, hyperchloremia was associated with increased morbidity, kidney dysfunction, and mortality in different studies.[27,28]

Finally, unlike other surgeries, once the resection is complete, patients undergoing HIPEC receive intraperitoneal chemotherapy such as with mitomycin or paclitaxel. These agents are associated with cytotoxicity and nephrotoxicity,[29] which can occur at much higher rates in hypovolemic patients. Furthermore, patients who develop acute kidney injury with cytoreductive surgery and HIPEC have higher rates of major morbidity and longer lengths of stay.[30]

The main limitations in our study are its retrospective design and that all interventions were performed by the same surgical team who performed very careful and prolonged resections with high fluid losses but with little blood loss. Although the involvement of a single team increased the internal validity of our study, our results may not extrapolate to all centers.

Conclusions

Our results showed that volume restriction is not a solution and could increase morbidity. Future randomized studies comparing goal-directed fluid therapy with moderate fixed fluid administration will be required. But, the trial will only be valid if adequate cardiac output is controlled and guaranteed in both groups, and a similar colloid/crystalloid ratio is used.

Conflicts of interests

The authors declare no conflicts of interest.

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