Original Article

Intravenous Dextrose Calories in Critically Ill Patients Requiring Vasopressor Therapy

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Objective: The hidden calories from non-nutritional sources should be considered when prescribing an energy target in intensive care unit (ICU). We aim to determine the calories acquired from intravenous dextrose in patients who required and did not require vasopressor therapy.

Materials and Methods: A retrospective study was conducted in a medical ICU. Administered intravenous dextrose grams were recorded for 7 days since the initiation of nutritional support. Daily and average intravenous dextrose calories were compared between vasopressor and non-vasopressor groups. Linear mixed model was used to assess the effect of the conditions requiring vasopressor therapy on intravenous dextrose calories.

Results: There were 93 and 129 patients in the vasopressor and non-vasopressor groups. On the first day of nutritional support, intravenous dextrose calories were 134 (interquartile [IQR] 60.4 to 246.7) and 73.6 (IQR 27.9 to 134.8) kcal/day for vasopressor and non-vasopressor groups respectively (p<0.001). Intravenous dextrose calories decreased over 7 days of nutritional support. The average of intravenous dextrose calories in the vasopressor group was higher than the non-vasopressor group (101.7 [IQR 47.8 to 160.3] vs. 56.3 [IQR 19.3 to 125.1] kcal/day, p=0.002). A multivariable linear mixed model showed that the conditions requiring vasopressor led to a significantly increase of intravenous dextrose calories by 40.1 kcal/day (95% CI 7.2 to 73.1).

Conclusion: The calories from intravenous dextrose in critically ill patients with vasopressor therapy was higher than that of patients who did not require vasopressor. The conditions requiring vasopressor therapy led to an increase of intravenous dextrose calories by 40 kcal/day.

Keywords: Dextrose; Vasopressor; Energy; Calorie; Critically ill

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Optimization of energy provision is a cornerstone of nutritional therapy in critically ill patients. While the effects of hypocaloric feeding on clinical outcomes remains an ongoing debate[1-7], overfeeding has been continuously shown to be associated with an increase of infection complications, metabolic derangements, and the needed duration of mechanical ventilation[8-10]. Many strategies have been proposed to prevent over-caloric nutrition support in the ICU. The current guidelines for nutritional management in critically ill patients recommend regular energy expenditure measurement by indirect calorimetry[11,12] instead of using energy expenditure predictive equations, which can lead to a large over-estimation[13]. Hidden calories from non-nutritional sources, namely propofol and intravenous dextrose, should be monitored closely when prescribing nutritional support as they can contribute to an unexpected overfeeding[14]. An observational study by Villet et al reported unintentional calories from non-nutritional sources ranged from 150 to 600 kcal/day when patients were not fed[15]. Propofol is well recognized regarding its fat-containing content in its preparation. It is generally infused in a predictable amount, which allows for daily calculation of its calories. On the other hand, the amount of intravenous dextrose infusion depends on patient's condition and comes from various sources, hence it is rather fluid and hard to predict. The data regarding the calories from intravenous dextrose in literature is limited. The aim of our study was to determine the calories from intravenous dextrose in critically ill patients during feeding. We further planned to assess whether, and to what extent, the conditions requiring vasopressor would increase intravenous dextrose calories as compared to the patients who needed no vasopressor in ICU.

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Materials and Methods

Study design and patient selection

We conducted a retrospective cohort study based on data prospectively collected by another observational study carried out in the medical ICU of Srinagarind hospital, Khon Kaen, Thailand. Our inclusion criteria were aged between 18 to 80 years old, admitted to the medical ICU for more than 72 hours. For the vasopressor group, the patients must have received any vasopressors treatment since the first day of ICU admission. For the non-vasopressor group, they must have received no vasopressor treatment since the first day of admission until the end of study period. Exclusion criteria were a lack of commitment to ongoing life support within 7 days after the initiation of nutritional support, pregnancy, or receiving no nutritional support during the entire ICU stay. The initial study began when a physician prescribed any calories as a nutritional support, e.g., start of an oral diet, enteral tube feeding, or parenteral nutrition. The medical records were reviewed up to 7 days after initiation of nutritional support or until the patients were discharged from ICU, according to which event occurred firstly. The study was approved by the Ethics Committee in Human Research, Khon Kaen University, Thailand (HE581481) and granted a waiver of informed consent.

Data collection

Demographic characteristics, including age, gender, body mass index, primary diagnosis, APACHE II score, SOFA score, mechanical ventilation status, vasopressor therapy status, route of nutritional support, duration of vasopressor use, hospital and ICU length of stay, mortality, were extracted from the case record forms of a previously conducted observational study that recruited consecutive patients admitted to ICU during August 2014 to April 2015.

Intravenous dextrose calories

Intravenous dextrose calories are calories derived from dextrose-containing fluid intravenously infused for other treatment purposes apart from nutritional support, e.g., intravenous vasopressor or antibiotics dissolved in 5% dextrose in water. The amount of dextrose in grams was calculated according to the concentration and volume of the solution infused per day and converted to kcal by multiplying with 3.4 kcal/g. Daily intravenous dextrose calories were recorded from the day that nutritional support was started until 7 days later (or until the patients were discharged from ICU up to which event occurred firstly).

Statistical analyses

Baseline data was presented in mean±standard deviation (SD) or median and interquartile range (IQR) for continuous variables. Categorical and nominal variables were expressed in counts and percentages. The daily intravenous dextrose calorie count and its average across a study period in vasopressor and non-vasopressor group were compared by Wilcoxon rank-sum test. An average of intravenous dextrose calories during the first 3 days and that of the day 4 to 7 of the same group were compared by Wilcoxon signed-rank test. The effect of the conditions requiring vasopressor therapy on intravenous dextrose calories was assessed by linear mixed model with a propensity score adjustment. The analyses were performed with R software version 3.2; The R Foundation for Statistical Computing Platform.

Sample size calculation

To achieve a power of 90% and level of significance at 0.05, a sample size of 62 patients was required to establish a mean of daily intravenous dextrose calories in each group. We estimated a 50% drop-out rate during the study period, therefore 124 patients per group were required. By using a data set with a repeated measurement of up to 7 times per patient, only 15 patients were needed for each arm to demonstrate a 100 kcal difference of intravenous dextrose calories between groups of patients who received and did not receive vasopressor.

Results

Of the 401 records of ICU patients admitted during August 2014 to April 2015 were reviewed. There were 245 records that met the inclusion criteria. Among these records, 22 were excluded because they did not receive nutritional support during their ICU stay and one record was excluded because of missing essential information. A total of 222 records, 1,516 study days, were included into our analysis. There were 93 and 129 records in the vasopressor and non-vasopressor groups, respectively. The baseline characteristics of the patients are shown in Table 1. A greater percentage of patients were diagnosed with severe sepsis as a primary condition requiring ICU stay in the vasopressor group. Median duration of vasopressor requirement was 4 (IQR 2 to 6) days. The two most frequently used vasopressors were norepinephrine and epinephrine. As the median duration of vasopressor use was shorter than the study period, there were also the study days without vasopressor in the vasopressor group. The patients in the vasopressor group received vasopressor in 51.7% of the total study days.

Nutritional support characteristics are described in Table 2. Nutritional support was started on a median of day 3 (IQR 2 to 4) and day 2 (IQR 2 to 3) of admission in the vasopressor and non-vasopressor groups respectively ($p<0.001$). 54% and 80% of patients received nutritional intervention within the second and third day of ICU admission, respectively. The majority of them (68%) were fed via enteral tube feeding, while there were only 3 (1.4%) patients prescribed with parenteral nutrition. 67% of patients received their feeding every day throughout the study period. The overall characteristics of nutritional support was not different between vasopressor and non-vasopressor group except starting day of nutritional support (Table 2).

Daily intravenous dextrose calorie intake was compared between vasopressor and non-vasopressor group. The vasopressor group received a significantly higher amount of daily intravenous dextrose calories than the non-

Table 1. Baseline characteristics

Characteristics	All (222)	Vasopressor (93)	Non-vasopressor (129)	p-value++
Age, median (IQR), years	59.5 (46 to 67)	62 (49 to 69)	59 (44 to 66)	0.121
Female, n (%)	89 (40.1)	39 (41.9)	50 (38.8)	0.736
BMI, median (IQR), kg/m^2	21.5 (18.6 to 24.7)	21.5 (18.7 to 25.1)	21.5 (18.5 to 24.2)	0.80
Diagnosis, n (%)				<0.001
Severe sepsis	47 (21.2)	41 (44.1)	6 (4.7)	
Pneumonia	49 (22.1)	22 (23.7)	27 (20.9)	
Heart failure	12 (5.4)	4 (4.3)	8 (6.2)	
Malignancy	6 (2.7)	0 (0)	6 (4.7)	
Liver cirrhosis	4 (1.8)	1 (1.1)	3 (2.3)	
Cardiac arrest	2 (0.9)	2 (2.2)	0 (0)	
Others	102 (46)	23 (24.7)	79 (61.2)	
APACHE II score, mean (SD), points	23.4±8	25.3±8	22±7.7	0.002
SOFA score	7.9±3.8	10.1±3.8	6.3±2.9	<0.001
Mechanical ventilation, n (%)	160 (72.1)	69 (74.2)	91 (70.5)	0.70
Duration of mechanical ventilation, median (IQR), days	7 (4 to 14)	10 (5 to 16)	6 (3.5 to 11)	<0.001
Renal failure, n (%)	165 (74.3)	75 (80.7)	90 (69.8)	0.09
Renal replacement therapy, n (%)	71 (32)	36 (38.7)	35 (27.1)	0.09
Duration of vasopressor, median (IQR), days	-	4 (2,6)	-	-
Type of vasopressor, n (%)				-
Norepinephrine	-	90 (97.8)	-	
Epinephrine	-	11 (12.0)	-	
Dopamine	-	13 (14.1)	-	
Dobutamine	-	7 (7.6)	-	
Total vasopressor days, n (%)+	-	353 (51.7)	-	-
ICU length of stay, median (IQR), days	8.5 (5 to 16)	11 (6 to 19)	7 (5 to 13)	<0.001
Hospital length of stay, median (IQR), days	19.5 (11 to 36)	22 (12 to 40)	18 (10 to 35)	0.07
ICU mortality, n (%)	36 (16.2)	27 (29.0)	9 (7)	<0.001
Hospital mortality, n (%)	62 (28.6)	37 (39.8)	25 (20.2)	0.003

APACHE = Acute Physiology and Chronic Health Evaluation; ICU = intensive care unit; IQR = interquartile range; SD = standard deviation; SOFA = Sequential Organ Failure Assessment
+ From a total of 1561 study days, there were 683 and 833 study days in vasopressor and non-vasopressor group, respectively
++ Comparing vasopressor and non-vasopressor group

vasopressor group throughout the study period (Table 3 and Figure 1). The average of intravenous dextrose calories during the study period in vasopressor group was also higher than that of the non-vasopressor group either in terms of kcal/day (101.7 [IQR 47.8 to 160.3] vs. 56.3 [IQR 19.3 to 125.1] kcal/day) or kcal/kg/day (1.70 [IQR 0.8 to 2.9] vs. 0.94 [IQR 0.4 to 2.4] kcal/kg/day). Further, the average of intravenous dextrose calories during the first 3 study days was significantly higher than that of the latter period (day 4 to 7) in both vasopressor and non-vasopressor groups. Multivariable analysis with propensity score adjustment showed that intravenous dextrose calories decreased significantly after the first day of nutritional support. The need of vasopressor significantly increased intravenous dextrose calories by a mean of 40.1 (95% CI 7.2 to 73.1) kcal/day (Table 4).

Discussion

To our knowledge, we are the first study conducted specifically dedicated to caloric intake from intravenous dextrose in the ICU. Many studies exploring the nutritional caloric provision in ICU patients made no mention as to whether they included non-nutritional calorie in their results[16-18]. As energy optimization in critically ill patients

Table 2. Characteristics of nutritional support

Characteristics	All (222)	Vasopressor (93)	Non-vasopressor (129)	p-value+
Day of admission that nutritional support was started, median (IQR)	2 (2 to 3)	3 (2 to 4)	2 (2 to 3)	<0.001
Day 1, n (%)	31 (14.0)	5 (5.4)	26 (20.2)	<0.001
Day 2, n (%)	90 (40.5)	30 (32.7)	60 (46.5)	
Day 3, n (%)	57 (25.7)	25 (26.9)	32 (24.8)	
Day 4, n (%)	27 (12.2)	18 (19.4)	9 (7.0)	
After day 4, n (%)	17 (7.7)	15 (16.1)	2 (1.6)	
Route of nutritional support, n (%)				
Oral diet	68 (30.6)	27 (29.0)	41 (31.8)	0.858
Enteral tube feeding	151 (68.0)	65 (69.9)	86 (66.7)	
Parenteral nutrition	3 (1.4)	1 (1.1)	2 (1.6)	
Number of days, which nutritional support was withheld, median (IQR), days	0 (0, 1)	0 (0, 1)	0 (0, 1)	0.154
No interruption, n (%)	149 (67.1)	59 (63.4)	90 (69.8)	0.131
1 day, n (%)	36 (16.2)	13 (14.0)	23 (17.8)	
2 days, n (%)	19 (8.6)	8 (8.6)	11 (8.5)	
3 days, n (%)	7 (3.2)	6 (6.5)	1 (0.8)	
≥4 days, n (%)	11 (5.0)	7 (7.5)	4 (3.1)	

IQR = interquartile range
+ Comparing vasopressor and non-vasopressor group

is crucial, non-nutritional calories should be given closer attention when planning for daily caloric prescription. We believe that our study would help in filling the current gap of knowledge.

It should be noted that there are studies addressing non-nutritional calories as a part of their results. However, they did not present them separately but included them in a summation of caloric intake[19-23]. A few studies clearly demonstrated intravenous dextrose calories in their manuscripts or supplementary appendices. Arabi, et al reported calories from intravenous dextrose in ICU patients of 117.1±105.6 and 114.1±101.4 kcal/day in patients receiving permissive underfeeding and full target feeding respectively[24]. Another study of Arabi, et al compared the effects of permissive underfeeding versus standard feeding in critically ill patients. Though there were no details about the exact amount of calories from intravenous dextrose in their publication, we can see from their figures that their means ranged from 30 to 60 kcal/day with a very wide confidence interval[2]. In comparison with our results, the intravenous dextrose calories on the first day of study period in vasopressor group was almost doubled from that of the latter study. This finding might be explained by 2 reasons. Firstly, the study of Arabi et al excluded the patients requiring high doses or a combination of vasopressors. We had 24.73% of patients in the vasopressor group received more than 1 vasopressor at a time (Table 1). Therefore, our surplus calories might represent dextrose from vasopressor(s) itself or the increment of intravenous fluid infusion related to the treatment of hypovolemia or shock. Secondly, physicians might have intentionally retarded the titration rate of enteral nutrition at the beginning if their patients still required vasopressor and allowed them to rely more on intravenous fluids than nutritional support. The rate of feeding progression could vary according to local feeding protocol or individuals where protocol has not been applied.

A significant decrease in intravenous dextrose calories was observed from day 1 onwards in both the vasopressor and non-vasopressor groups. An average of intravenous dextrose calories during the early period was significantly higher than that of the late period in both groups. These findings might represent a tapering-off of vasopressor (in vasopressor group) and intravenous fluid intake while enteral nutrition or oral diet was being stepped up. As the patients progress more on feeding titration, the necessity of intravenous fluid declines. We found that our intravenous dextrose calories from day 2 to day 7 were close to those in literatures. The lower border of their results was concordant with our non-vasopressor group, and their higher border was closed to those of our vasopressor group. Again, the findings suggested that the conditions requiring vasopressor might lead to an increased amount of intravenous dextrose infusion.

The result of our multivariate analysis showed that the conditions requiring vasopressor therapy contributed to

Table 3. Daily intravenous dextrose calories in vasopressor and non-vasopressor groups

Intravenous dextrose calories	Vasopressor⁺ (kcal)	Non-vasopressor⁺ (kcal)	p-value
Day 1, kcal	134 (60.4 to 246.7)	73.6 (27.9 to 134.8)	<0.001
Day 2, kcal	69.1 (24.4 to 159.5)	38 (0 to 107)	<0.001
Day 3, kcal	67.2 (17.0 to 142.5)	32 (0 to 115.1)	0.011
Day 4, kcal	62.4 (17.0 to 147.2)	19.6 (0 to 91.1)	0.009
Day 5, kcal	63.8 (19.2 to 211.9)	17 (0 to 116.8)	0.007
Day 6, kcal	69.2 (17.0 to 173.9)	20.2 (0 to 130)	0.010
Day 7, kcal	66.3 (22.10 to 177.14)	18.9 (0 to 95.5)	0.013
Average (day 1 to 7)			
Kcal/day	101.7 (47.8 to 160.3)	56.3 (19.3 to 125.1)	0.002
Kcal/kg/day	1.7 (0.8 to 2.9)	0.9 (0.4 to 2.4)	0.003
Early period (day 1 to 3)			
Kcal/day	109 (54.1 to 180.3) *	70 (26 to 135.5) ***	0.001
Kcal/kg/day	1.86 (1.0 to 3.2) **	1.12 (0.5 to 2.5) ****	0.002
Late period (day 4 to 7)			
Kcal/day	60.6 (19.8 to 140.7) *	17 (0 to 105.8) ***	0.001
Kcal/kg/day	1.1 (0.4 to 2.3) **	0.32 (0 to 1.8) ****	0.002

⁺ Values are expressed in median and interquartile range. Number of patients were 93 and 129 for Day 1, 92 and 129 for Day 2, 89 and 122 for Day 3, 81 and 104 for Day 4, 68 and 76 for Day 5, 62 and 69 for Day 6, and 53 and 57 for Day 7 in vasopressor and non-vasopressor groups, respectively.
*,**p<0.01 compare between early (Day 1 to 3) and late period (Day 4 to 7) in the vasopressor group.
***, ****p<0.01 compare between early (day 1 to 3) and late period (day 4 to 7) in the non-vasopressor group

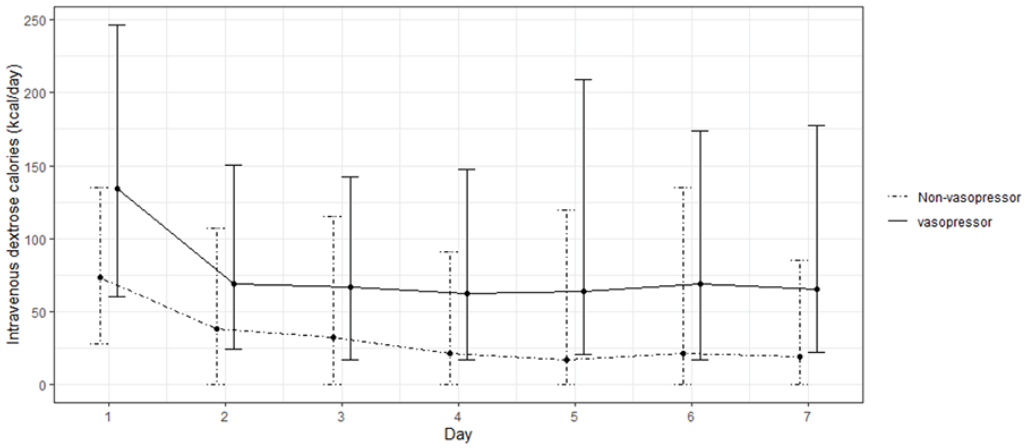

Figure 1. Median and interquartile range of intravenous dextrose calories of patients in vasopressor and non-vasopressor group.

a significant increase of intravenous dextrose calories for 40 kcal/day which can be converted to an additional infusion of 5% dextrose solution of 235 ml/day or 9 to 10 ml/hour. This incremental effect was much lower than expected. We were able to demonstrate a statistical significance despite a small difference between groups. This could be a result of using a study population 6 times larger than what we initially proposed to detect the difference between groups in linear mixed model analysis. Whether this number of additional calories will have clinical significance needs a further

Table 4. Bivariate and multivariate linear mixed model analyses for the effect of conditions requiring vasopressor therapy on intravenous dextrose calorie (kcal)

Variables	Bivariable analysis		Multivariable analysis[+]	
	β (95% CI)	p-value	β (95% CI)	p-value
Interception	117.2 (96.3 to 138.1)	<0.001	174.78 (111.3 to 238.3)	<0.001
Vasopressor	41.22 (16.6 to 65.9)	0.001	40.13 (7.2 to 73.1)	0.019
Study day				
Day 1	-	-	-	-
Day 2	-41.3 (-62.7 to -20.0)	<0.001	-120.1 (-150.9 to -89.3)	<0.001
Day 3	-38.6 (-60.3 to -17.0)	0.001	-115.0 (-146.1 to -83.8)	<0.001
Day 4	-54.0 (-76.5 to -31.4)	<0.001	-130.2 (-162.0 to -98.3)	<0.001
Day 5	-36.8 (-61.3 to -12.3)	0.004	-113.6 (-147.1 to -80.1)	<0.001
Day 6	-52.1 (-77.4 to -26.9)	<0.001	-127.0 (-161.2 to -92.8)	<0.001
Day 7	-51.1 (-78.0 to -24.3)	<0.001	-127.7 (-163.3 to -92.1)	<0.001
Propensity score	-	-	86.5 (22.6 to 150.4)	0.009

[+] Adjusted for age, gender, principal diagnosis, and propensity score

exploration.

To avoid overfeeding in ICU, it should be kept in mind that when prescribing calories for critically ill patient, the target calories should be subtracted by non-nutritional calories from 2 sources, namely propofol and intravenous dextrose[12], especially for those with low body mass index who are prone to overfeeding. Arabi et al showed that usage of a propofol infusion can cost calories up to 100 kcal/day[2]. Hence, physicians should be aware of and calculate calories according to the planned amount of propofol infused. On the other hand, calculation of actual calories from intravenous dextrose might be burdensome. Based on our results, we propose that a 140 and 100 kcal/day would be a reasonable amount representing all intravenous dextrose calories for patients who require vasopressor or not respectively. With this amount subtracted from target energy, which is roughly the 75th percentile of intravenous dextrose calorie for each group in our study, it should reduce the chance of overfeeding caused by these hidden calories in most of the patients. A minute over-subtraction occurred in some cases but should be considered acceptable as the current trend of nutritional support in ICU favors a slightly hypocaloric strategy, particularly in the first 7 days of admission[11,12]. Another solution to handle the calories from non-nutritional sources is an implementation of computerized information system (CIS). Many studies in the modern ICU rely on the CIS on collecting daily and cumulative energy balance[9,19-21,25]. The use of CIS has been proven to help in tracing hidden calories from various sources in the ICU setting, providing accurate information on energy balance which might lead to early detection of under- and overfeeding in ICU[26].

We believe that the retrospective design of this study would truly reflect real life practice and proved suitable for our research questions. We used a propensity score to deal with the unbalanced covariates that arose from non-randomization design. Our sample size was enough to achieve the level of significant at 0.05 on establishing the means of intravenous dextrose calories in ICU patients for almost the entire study except for day 7, due to the patients number being slightly lower than what we had proposed. The main limitation of our study is generalizability. Firstly, our study was conducted in a single medical ICU. The practice of intravenous fluid delivery can vary across institutes. Whether surgical critically ill settings will have any differences in this aspect remains to be explored. Secondly, we found a surprisingly low number of parenteral nutrition (PN) prescription in our ICU. Data from observational studies reported a rate of PN usage was around 13 to 25% of ICU patients[27-29]. Usually when patients are placed on PN, either as total PN or supplemental PN, it replaces the need for intravenous dextrose solution. Therefore, in the presence of PN, intravenous dextrose caloric intake would be substantially decreased. Our results were mostly obtained from patients receiving an oral diet or tube feeding. So, its generalizability is restricted.

Conclusion

The median of intravenous dextrose calories in critically ill patients during feeding was 101.71 and 56.34 kcal/day in patients who required and did not require vasopressor respectively. The conditions demanding vasopressor therapy led to a 40-kcal increase of intravenous dextrose calories per day. Whether these amounts of caloric differences will bring out any clinical importance has yet to be determined and further investigation is needed.

What is already known on this topic?

The hidden calories from non-nutritional sources

should be considered when prescribing an energy target in ICU. Literature reports a very wide range of non-nutritional calories without mention of their sources. Knowing the amount of calories from specific non-nutritional sources would help in a tailor-made nutritional prescription in ICU.

What this study adds?

The mean of intravenous dextrose calories in ICU patients without vasopressor therapy was 56.34 kcal/day. An additional of around 40 kcal/day is the surplus energy of dextrose from vasopressor(s) therapy for the patients who require them.

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Potential conflict of interest

The authors declare no conflict of interest.

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