Research Article

Sustained low-efficiency dialysis in septic shock: Hemodynamic tolerability and efficacy

Shakti Bedanta Mishra, Ratender Kumar Singh, Arvind Kumar Baronia, Banani Poddar, Afzal Azim, Mohan Gurjar

Abstract

Aim of the Study: Acute kidney injury (AKI) in septic shock has poor outcomes. Sustained low-efficiency dialysis (SLED) is increasingly replacing continuous renal replacement therapy as the preferred modality in Intensive Care Units (ICUs). However, the essential aspects of hemodynamic tolerability and efficacy of SLED in septic shock AKI has been minimally studied. **Patients and Methods:** We describe hemodynamic tolerability using modified vasopressor index (VI) and vasopressor dependency (VD) and efficacy using a combination of Kt/v, correction of acidosis, electrolyte, and fluid overload. Adult ICU patients of septic shock in AKI requiring SLED were included in this study. **Results:** One hundred and twenty-four patients of septic shock AKI requiring SLED were enrolled in the study. There were 74 nonsurvivors (NSs). Approximately, 56% (278/498) of the sessions in which vasopressors were required were studied. Metabolic acidosis (49%) was the predominant indication for the initiation of SLED in these patients. Baseline characteristics between survivors and NSs were comparable, except for age, severity scores, AKI stage, and coexisting illness. VI and VD prior to the initiation of SLED and delta VI and VD during SLED were significantly higher in NSs. Hemodynamic tolerability and efficacy of SLED was achievable only at lower vasopressor doses. **Conclusion:** VI, VD, and combination of Kt/v together with correction of acidosis, electrolyte, and fluid overload can be used to describe hemodynamic tolerability and efficacy of SLED in septic shock AKI. However, at higher vasopressor doses in septic shock, hemodynamic tolerability and efficacy of SLED requires further evidence.

Keywords: Acute kidney injury, efficacy of dialysis, hemodynamic tolerability, septic shock, sustained low-efficiency dialysis

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Introduction

Acute kidney injury (AKI) is a common clinical syndrome with varied etiology. It may complicate approximately 5% and 30% of hospital and Intensive Care Unit (ICU) admissions, respectively.[1] AKI associated with sepsis has a high mortality ranging from 50% to 70%.[2,3] Renal replacement therapy (RRT) is an important component of its management in ICU. RRT is usually performed as intermittent hemodialysis (IHD) or continuous RRT (CRRT). Each of these modalities has their specific benefits and limitations. A "hybrid" form of RRT-sustained low-efficiency dialysis (SLED) has gained popularity over years. SLED has most of the advantages of IHD and CRRT. Experience of peritoneal dialysis in AKI is limited.

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Selecting the optimum RRT in septic shock is challenging.[4] The Kidney Disease Improving Global Outcomes (KDIGO) guidelines of 2012 suggested CRRT for hemodynamically unstable and acute brain injury patients.[5] However, SLED is increasingly being preferred over CRRT in the ICUs on account of reduced exposure to anticoagulation and shorter down time compared to CRRT. Schwenger *et al*.[6] in the largest randomized control trial comparing both concluded that SLED while having similar outcomes had both reduced cost and nursing requirements. Despite its popularity, literature about its use and efficacy in patients of AKI with septic shock is limited. Furthermore, aspects of hemodynamic tolerability and efficacy of SLED in this difficult subset of patients have been sparingly addressed.

Thus, this present study was conducted with the aim to describe hemodynamic tolerability and efficacy of SLED in AKI patients with septic shock.

Patients and Methods

Study population

We conducted a prospective, observational study in a single-center 12-bed medical-surgical ICU. The study was conducted from 2013 to 2015, after being approved by the Institute's Ethics Committee. Informed written consent from patients or their first of kin was taken prior to inclusion in the study. Consecutive adult patients (≥18 years) in septic shock with AKI and requiring RRT were included in the study. Patients with recent neurosurgery, known or suspected raised intracranial pressure, and pregnancy were excluded from the study.

Definitions

Septic shock was defined and managed according to the Surviving Sepsis Campaign guidelines of 2012.[7]

AKI was defined according to the KDIGO definition of 2012.[5]

Source of sepsis was defined as respiratory, intra-abdominal, hematological, urinary, others (tropical and skin and soft tissue), or unknown based on evidence or clinical suspicion.

Dialysis

Fresenius 2008S dialysis machine and Fresenius AV600S 1.4 m^2 membranes were used in the study. Heparin dosing, blood flow, ultrafiltration rate, and the frequency of RRT were decided by a nephrologist in consultation with the intensivist. Requirement for dialysis and switching from one to another modality of RRT was as per the decision of the intensivist and nephrologist.

Hemodynamics

Hemodynamic status during RRT was defined by vasopressor index (VI) and vasopressor dependency (VD). VI was calculated by the following formula:

([dopamine dose × 1] + [dobutamine dose × 1] + [adrenaline dose × 100] + [noradrenaline dose × 100] + [vasopressin dose × 10]).

All doses were in μg/kg/min except vasopressin which was in units/hour. We modified the VI[8-10] to include vasopressin in place of phenylephrine as vasopressin is the most commonly used vasopressor after noradrenaline in septic shock. VD was calculated by the following formula:

(VI/Mean arterial pressure [MAP]) × 100.

The delta (Δ) VI and ΔVD were calculated by the difference between the predialysis values and the highest values recorded during the dialysis session.

Hemodynamic tolerability

Patients on vasopressors were considered hemodynamically unstable. However, defining hemodynamic tolerability during SLED in such patients is not clear. In our study, we have defined hemodynamically intolerable session as ΔVD of 20 and above.

Efficacy of sustained low-efficiency dialysis

Efficacy of SLED in our study was determined by modified Daugirdas formula for Kt/v ($-\ln [R - 0.03] + [4 - 3.5R]\, UF/W$), where R is the ratio of post/predialysis blood urea nitrogen (BUN), *UF* is the total ultrafiltrate volume in liters/dialysis, and *W* is the patient's weight in kilograms,[11] correction of hyperkalemia (≤4.5 mEq/L), correction of metabolic acidosis (base deficit of ≤5 mEq/L) and fluid balance over the entire duration of dialysis. Daily fluid balance was defined as the total fluid intake from all sources (intravenous fluids and blood products, enteral and parenteral nutrition, and medications) minus the output from all sources (urine, ultrafiltrate, and output from drains). Since the gastrointestinal losses (stool volume) were not quantified, they were not included in calculations. We calculated mean daily fluid balance for the entire dialysis period for analysis.

Clinical profile

The demographic (age, gender, source of sepsis), severity (Acute Physiology and Chronic Health Evaluation [APACHE-II], Sequential Organ Failure Assessment [SOFA]) score, hemodynamic profile, and efficacy of SLED were studied in all the patients. Patients were categorized into survivors (Ss) and nonsurvivors (NSs) in terms of survival at day 28.

Statistical analysis

Data were expressed as median (interquartile range [IQR]) or proportions as appropriate. Comparison between Ss and NSs was done using Mann–Whitney test for continuous data and Fisher's exact test for proportions. After univariate analysis, the factors found significant were subjected to further multivariate analysis to determine the independent predictors of mortality. Receiver operating characteristic (ROC) of area under curve (AUC) was done for predialysis VD to predict a hemodynamically intolerable session. A two-tailed $P < 0.05$ was considered statistically significant. Statistical software SPSS version 21 (SPSS Inc., Chicago IL, USA) for Windows was used for analyzing the data.

Results

Out of a total of 554 patients admitted to our ICU, 430 did not meet the inclusion criteria [Figure 1]. Following were the reasons for exclusion: ~16% (69/430) were pediatric patients (<18 years), 49% (212/430) were not in septic shock, and 35% (149/430) were in AKI not requiring RRT. Finally, we were able to recruit 124 adult patients (male:female = 86:38) of septic shock. A total of 498 sessions of SLED were conducted in these patients recruited in the study. All the 124 patients underwent at least one session of SLED during their ICU stay. Some of the sessions were done after the patient had recovered from septic shock. In our analysis of hemodynamic tolerability and efficacy, we included only 278 of 498 (~56%) sessions which required vasopressors. Sessions without vasopressors (220/498; ~44%) were excluded from the analysis.

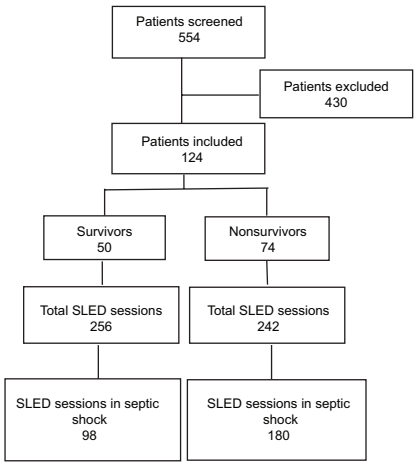

Figure 1: Flow diagram showing patient recruitment and outcome

Clinical profile

The baseline characteristics of the study population were as depicted in Table 1. The age distribution of the patients, severity indices, APACHE-II, SOFA scores, and stage of AKI on initiation of SLED differed significantly between the NSs and Ss. Diabetes mellitus, hypertension, and chronic obstructive pulmonary disease were significantly higher in NSs. Respiratory followed by intra-abdominal site was the most common source of sepsis. The laboratory parameters were comparable.

Hemodynamics and sustained low-efficiency dialysis

The parameters prior to each SLED session were shown in Table 2. Significantly, a greater number of sessions requiring vasopressors were observed in NSs (74% [180/242] vs. 38% [98/256] in Ss, $P < 0.01$). NSs had a significantly higher VI and VD ($P < 0.01$) prior to the initiation of SLED. The ΔVI and ΔVD were significantly higher in NSs ($P = 0.01$ and 0.03, respectively). Significantly, a higher percentage of hemodynamically intolerable SLED sessions were observed in NSs (~31%; $P < 0.01$) [Table 3].

Efficacy of sustained low-efficiency dialysis

The NSs had significantly lower creatinine ($P < 0.01$) and BUN levels ($P < 0.01$). Acid–base parameters were comparable between groups [Table 2]. A median of three SLED sessions were required in 124 patients [Table 3]. Metabolic acidosis (49%) was the predominant indication for the initiation of RRT. The duration of SLED session, ultrafiltration achieved, and blood and dialysate flow were comparable in Ss and NSs. The dose of SLED calculated by Kt/v was significantly lower in NSs ($P < 0.01$). Correction of metabolic acidosis was more effective in Ss ($P < 0.01$), while correction of hyperkalemia was comparable. Metabolic acidosis was the indication for dialysis in 49 of 70 (70%) hemodynamically intolerable sessions. However, its correction was not achievable in 45% (22/49) as compared to 14% (12/87) of hemodynamically tolerable sessions, $P < 0.001$. Cumulative fluid balance was significantly lower in Ss ($P = 0.01$).

Predictors of hemodynamic intolerable sessions and mortality

The AUC ROC for predialysis VD with hemodynamically intolerable SLED session as classification variable was 0.80 (95% CI: 0.74–0.87, $P < 0.001$) [Figure 2]. Optimum single cutoff value of VD ≥ 25 yielded sensitivity and

Table 1: Baseline characteristics of the study population

Variables	Total (*n*=124)	Survivors (*n*=50)	Nonsurvivors (*n*=74)	*P*
Age, years	52 (32-62)	38 (23-60)	53 (35-62)	0.04*
Female, *n* (%)	38 (31)	16 (42)	22 (58)	0.84
Severity scoring				
APACHE II	24.5 (18-28)	23 (15-27)	25 (20-29)	0.01*
SOFA	12 (10-15)	11 (9-13)	14 (10-16)	<0.001**
AKI stage, *n* (%)				0.01*
1	12 (10)	2 (17)	10 (83)	
2	22 (18)	14 (64)	8 (36)	
3	90 (72)	34 (38)	56 (62)	
Comorbidities, *n* (%)				
Diabetes mellitus	52 (42)	8 (15)	44 (85)	0.01*
COPD	14 (11)	2 (14)	12 (86)	0.04*
Hypertension	44 (35)	12 (27)	32 (73)	0.01*
IHD	6 (5)	4 (67)	2 (33)	0.21
Immunocompromised	4 (3)	0 (0)	4 (100)	0.08
Source of sepsis, *n* (%)				0.14
Respiratory	68 (55)	30 (44)	38 (56)	
Intra-abdominal	40 (32)	12 (30)	28 (70)	
Hematological	2 (2)	0 (0)	2 (100)	
Others	12 (9)	6 (50)	6 (50)	
Unknown	2 (2)	2 (100)	0 (0)	
Laboratories				
Hemoglobin (g/dl)	9.8 (8.4-10.9)	9.7 (8.4-10.9)	10 (8-11.4)	0.98
TLC ($\times 10^3/\mu L$)	13.7 (10.3-19.9)	14.6 (10-17)	13.2 (9-23.3)	0.66
Platelet ($\times 10^3/\mu L$)	88 (52-164)	99 (65-175)	79 (40-139)	0.08
aPTT (s)	30 (27-42)	31 (28-44)	29 (27-40)	0.28
Prothrombin time (s)	17 (16-24.4)	18 (17-25)	17 (15-20)	0.09
Pro-calcitonin (ng/mL)	13 (2.9-44.9)	26 (2-77)	10 (25-31.5)	0.42

Data measurements are in median (interquartile range) unless specified. *Significant $P<0.05$. **Highly significant $P<0.001$. APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; COPD: Chronic obstructive pulmonary disease; IHD: Ischemic heart disease; TLC: Total leukocyte count; aPTT: Activated partial thromboplastin time

Table 2: Variables prior to initiation of sustained low-efficiency dialysis in patients with septic shock

Variables	Total sessions (*n*=278)	Sessions in survivors (*n*=98)	Sessions in nonsurvivors (*n*=180)	*P*
Creatinine (mg/dl)	3 (1.9-4.2)	3.6 (3-5.1)	2.2 (1.7-3.9)	<0.01*
Blood urea nitrogen (mg/dl)	76 (54-99)	83 (69-99)	65 (48-98)	<0.01*
pH	7.36 (7.30-7.40)	7.35 (7.30-7.39)	7.36 (7.30-7.41)	0.27
Bicarbonate (mEq/L)	21 (17.5-24.6)	19.2 (17-22.3)	22 (17-25)	0.01*
Base deficit (mEq/L)	4 (0.2-8.7)	5 (2.1-9)	3 (0.6-8)	0.005*
Potassium (mEq/L)	4 (3.6-4.6)	4.3 (3.7-4.8)	4 (3.5-4.6)	<0.01*
Sodium (mEq/L)	134.5 (131-138)	132 (129-136)	135 (132-141)	0.01*
Mean arterial pressure mmHg	82 (74-89)	83 (76-92)	81 (73-88)	0.34
VI	20 (8-40)	11 (6-32)	26.5 (10-44)	<0.01*
VD (/mmHg)	23 (10-48)	16 (6.7-36)	33.3 (12.5-53)	<0.01*

Data measurements are in median (interquartile range) unless specified. *Significant $P<0.05$. VI = ([dopamine dose×1] + [dobutamine dose×1] + [adrenaline dose×100] + [noradrenaline dose×100] + [vasopressin dose×10]). All doses are in μg/kg/min except that of vasopressin which is in units/hours. VD = (VI/MAP) × 100. VI: Vasopressor index; VD: Vasopressor dependency

specificity of approximately 83% and 67%, respectively. Factors associated with mortality were diabetes mellitus, SOFA score, and VD at the initiation of SLED. Factors such as diabetes mellitus, SOFA ≥ 12, and VD ≥ 25 after dichotomization were subjected to multivariate analysis for identifying predictors of mortality. Odds ratio was 13.3 (P = 0.001), 7 (P = 0.007), and 1.2 (P = 0.80) for diabetes mellitus, SOFA ≥ 12, and VD, respectively.

Discussion

SLED is an attractive option for the management of AKI in ICU. Despite its increasing popularity, studies supporting its hemodynamic tolerability and efficacy during septic shock are limited. Our study aimed to describe both the above issues during the implementation of SLED in septic shock patients. We will first focus on hemodynamics.

Hemodynamics and sustained low-efficiency dialysis

Hemodynamic tolerance to RRT in septic shock is a major concern. However, the very definition of hemodynamic tolerability in literature is quite variable. Several definitions have been used in studies comparing IHD or SLED with CRRT.[12] Defining hemodynamic

Table 3: Hemodynamic tolerability and efficacy of the sustained low-efficiency dialysis sessions in septic shock

Variables	Total patients (*n*=124)	Survivors (*n*=50)	Nonsurvivors (*n*=74)	*P*
SLED				
Total sessions (*n*)	278	98	180	<0.01*
Sessions per patient	3 (1.7-6.5)	3 (2-10)	3 (1-5)	0.11
Time to SLED (days)	1 (0-5)	0 (0-2)	1 (0-6.5)	0.23
Duration of sessions (h)	6 (4-8)	6 (5-8.5)	6 (4-8)	0.06
Ultrafiltrate (L)	1.5 (1-1.5)	1.5 (1-2)	1.4 (0.8-1.5)	0.03*
Blood flow (ml/min)	174 (154-196)	180 (155-210)	172 (150-192)	0.06
Dialysate flow (ml/min)	254 (218-278)	262 (223-281)	253 (214-276)	0.07
Hemodynamics				
ΔVI	5 (1-13)	4 (0.5-10)	5 (2-15)	0.01*
ΔVD (/mmHg)	6.4 (2.2-20)	5.5 (2.3-13.2)	8.6 (2.2-24.3)	0.03*
Hemodynamically intolerable session, *n* (%)	70 (25)	14 (14)	56 (31)	<0.01*
Indication of dialysis, *n* (%)				0.11
Metabolic acidosis	136 (49)	56 (57)	80 (45)	
Hyperkalemia	48 (17)	20 (20)	28 (16)	
Fluid overload	94 (34)	22 (28)	72 (40)	
Efficacy				
Kt/v	0.83 (0.59-1.13)	1.1 (0.7-1.3)	0.75 (0.5-1.01)	<0.01*
Correction of				
Base deficit, *n* (%)#	102 (75)	54 (96)	48 (60)	<0.01*
Potassium, *n* (%)#	48 (100)	20 (100)	28 (100)	1.0
CFB (ml/day)	870 (560-980)	675 (552-983)	900 (560-1150)	0.01*

Data measurements are in median (interquartile range) unless specified. *Significant *P*<0.05; #Percentage of corrected base deficit, potassium in patients with metabolic acidosis and hyperkalemia as indications for dialysis. SLED: Sustained low-efficiency dialysis; ΔVI: Delta vasopressor index; ΔVD: Delta vasopressor dependency; CFB: Cumulative fluid balance

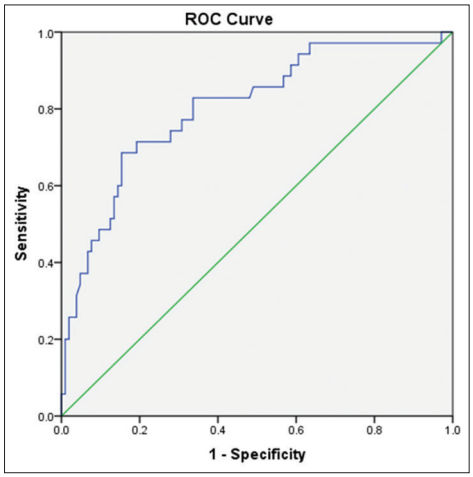

Figure 2: Receiver operating characteristic curve of vasopressor dependency prior to the initiation of dialysis

instability by a decrease in MAP singularly is not very informative in septic shock patients already on vasopressors. The recent meta-analysis comparing SLED and CRRT also raised this issue and commented that no meaningful data about hemodynamic instability was extractable from any of the included studies.[13] Our study attempts to address this major issue. We have used a more objective and comparable concept of VI and VD. Both these concepts have been used previously.[10] However, we have modified the VI by replacing vasopressin instead of phenylephrine which is less often used in septic shock. VD and Δ VD effectively nullify the distorting effect of MAP on the measurement of hemodynamic instability. VD may be used in the stratification of severity in septic shock.

To the best of our knowledge, this is perhaps the first study which attempts to describe the issue of hemodynamic tolerability of SLED specifically in septic shock. Kielstein *et al*.[14] compared SLED (*n* = 20) and CRRT (*n* = 19) in critically ill ventilated patients in AKI. This randomized study which included 85% patients of sepsis examined hemodynamic tolerability in terms of variability in heart rate, MAP, cardiac output, and systemic vascular resistance. Correction of metabolic acidosis during the course of dialysis was their end point. No difference was observed between SLED and CRRT. Vasopressor dose was increased (*n* = 5 each), unchanged (*n* = 5 and 3), and decreased (*n* = 10 and 11) in SLED and CRRT, respectively. Directional vasopressor trends were not quantified as in our study. Fieghen *et al*.[15] examined hemodynamic stability in a mixed group (*n* = 77) of critically ill patients. Hemodynamic instability was defined as reduction in MAP > 20% or escalation in vasopressor dose. The study inferred that SLED (39 sessions in 13 patients) was comparable to CRRT (86 sessions in 30 patients) in critically ill patients. However, in their study, only 70% of their patients were in shock, and even among them, not all were in septic shock. Furthermore, mean/median dose of noradrenaline was also not mentioned. Although their patients during SLED had higher episodes of hemodynamic instability (38.5 vs. 18.6% in CRRT), the requirements for vasopressor

escalation were more in CRRT (39.5 vs. 25.6% in SLED). Baldwin *et al*.[16] in a randomized controlled trial of 16 patients comparing SLED with CRRT concluded that SLED was more effective in fluid removal, despite lower MAPs in critically ill patients. No significant difference was observed between groups for heart rate, central venous pressure, and noradrenaline dose.

We have described hemodynamics in terms of VI/ΔVI and VD/ΔVD. The VD as well as SOFA was significantly higher in NSs on the initiation of SLED. ΔVI, ΔVD, and proportion of hemodynamically intolerable sessions were significantly higher in NSs. The plausible explanation for this result is that patients with higher preinitiation vasopressor requirements also had greater hemodynamic worsening during SLED. Since VD ≥ 25 has a good sensitivity, albeit only modest specificity, it may be used as a predictor of a hemodynamically intolerable SLED session. In the multivariate analysis, VD was not found to be an independent predictor of mortality. However, we need large studies (SLED vs. CRRT) in the specific group to establish the safety of SLED.

Efficacy of sustained low-efficiency dialysis

Efficacy of a dialysis session is mainly denoted by its dosing, i.e. by the Kt/v. Daugirdas's second-generation estimate of urea clearance has been validated in SLED sessions.[17] Since control of urea is one of the most important aspects of management of chronic renal disease, Kt/v is better suited to this population as compared to AKI. In AKI, patients mostly undergo dialysis for control of metabolic acidosis, fluid management, and/or hyperkalemia. Statistically significant but not clinically apparent baseline differences in the predialysis values were observed in Ss, probably on the account of being healthier and with greater muscle mass. However, there is minimal literature about comparison of these parameters. In this study, we have attempted to describe the efficacy of SLED by inclusion of correction of acidosis, hyperkalemia, and fluid management along with Kt/v. Silversides *et al*.[18] demonstrated fluid balance during dialysis as a predictor of mortality in AKI. Our results also show a correlation of fluid balance during dialysis with mortality. SLED also demonstrated better overall efficacy in the correction of these parameters in the Ss.

Predictors of hemodynamic intolerable sessions and mortality

Mortality is influenced by a variety of factors in critically ill patients of septic shock. SLED may be one of these factors or the need for SLED might just reflect the degree of organ dysfunction and/or coexisting illness. Our results are also reflective of this fact. VD ≥25 may be used for predicting a hemodynamically intolerable dialysis session in septic shock AKI.

Limitations

There exist several limitations in our study. Major ones include (1) single-center study, (2) small sample size, (3) observational design, (4) absence of a comparator arm of CRRT, (5) no comparison with nonseptic shock AKI patients on SLED, and (6) a relatively shorter duration of SLED. However, despite these shortcomings, we have attempted to objectively better define hemodynamic tolerability and efficacy of SLED in septic shock AKI. We humbly suggest that in future VD may be used as an essential parameter in the description of hemodynamics in septic shock AKI patients requiring dialysis.

Conclusion

VI, VD, and delta changes in these indices can be used to describe hemodynamics during RRT in septic shock AKI patients. SLED continues to be an attractive dialysis modality in septic shock AKI, albeit at lower vasopressor doses. Both its efficacy and hemodynamic tolerability are questionable at higher doses.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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