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Comparison of rocuronium and succinylcholine on postintubation sedative and analgesic dosing in the emergency department

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Objectives Rocuronium and succinylcholine are both commonly used neuromuscular blockers for rapid sequence intubation in the emergency department (ED). The objective of this study was to determine if patients who receive rocuronium are more likely to receive lower doses of postintubation sedatives and analgesics compared with patients who receive succinylcholine.

Methods This was a retrospective cohort study carried out in a tertiary, academic ED. Consecutive adult patients, who were intubated using etomidate for induction of sedation, were included. Patients were categorized on the basis of whether they received (a) rocuronium or (b) succinylcholine for paralysis. The dosing of postintubation sedative and analgesic infusions were compared 30 min after initiation between the two groups.

Results A total of 254 patients were included in the final analysis (rocuronium=127 and succinylcholine=127). In the overall cohort, 90.2% ($n=229$) of patients were administered a sedative postintubation in the ED. Most of these patients were initiated on propofol infusions. The mean propofol infusion rate at 30 min was 30 ± 23 mcg/kg/min in the rocuronium group and 42 ± 24 mcg/kg/min in the succinylcholine group ($P=0.002$). A total of 42.5%

of patients ($n=108$) received an analgesic infusion (all patients received fentanyl). The mean fentanyl infusion rate at 30 min was 0.65 ± 0.55 and 0.86 ± 0.49 mcg/kg/h in the rocuronium and succinylcholine groups, respectively ($P=0.041$).

Conclusion Patients who receive rocuronium are more likely to receive lower doses of sedative and analgesic infusions after intubation. This may place them at risk of being awake under paralysis. *European Journal of Emergency Medicine* 21:206–211 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Succinylcholine and rocuronium are the most commonly used paralytic agents for performing rapid sequence intubation (RSI) in the emergency department (ED) [1]. Comparative studies of these agents have historically focused on outcomes such as intubation conditions and success rates [2,3]. However, a recent study showed that paralytic selection also influenced postintubation care, such as the time to provision of sedation [4]. Patients administered rocuronium had greater delays in receiving postintubation sedatives. This is because rocuronium has a duration of action of greater than 45 min compared with succinylcholine, which has a duration of less than 6 min [5,6]. Therefore, the adequacy of sedation could be assessed sooner after intubation. However, it is possible that patients administered rocuronium also receive lower doses of sedatives and analgesics once these are initiated.

If left untreated after intubation, patients will begin to awaken after the effect of the induction agent wears off.

Etomidate is the commonly used induction agent and has a short duration of effect that is similar to succinylcholine [7]. Therefore, sedation and analgesia use after succinylcholine is titrated to patient response. However, after rocuronium, patients remain pharmacologically paralyzed for a prolonged period, during which pain and sedation level are difficult to assess and titration of medications that may be required for appropriate analgesia and sedation may not occur. Untreated pain and anxiety can lead to increased catecholamine release, hypercoagulability, immunosuppression, myocardial ischemia, increased oxygen requirements, increased intracranial pressure, and barotraumas [8].

Previous studies have shown that patients who undergo RSI in the ED often receive inadequate sedation and analgesia [9–11]. However, this problem may be potentiated in patients administered long-acting paralytics, such as rocuronium. We hypothesized that patients administered rocuronium for RSI would receive lower

doses of sedatives and analgesics after RSI compared with patients intubated using succinylcholine. Therefore, the primary objective of this study was to compare rocuronium and succinylcholine with respect to sedative and analgesia dosing after RSI.

Methods

Study design and setting

This was a retrospective cohort study carried out at a tertiary, academic ED in the USA. The ED has 61 beds, with an annual census of 70 000 patients. All medications used in this study were available in controlled access cabinets (Pyxis, San Diego, California, USA) located in the ED. The ED also had RSI kits, which included paralytics (rocuronium and succinylcholine) and etomidate that could be used for RSI. The selection and dosing of all medications was based on clinician preference. The hospital did not have any set protocol for medication use in this setting. Most intubations at our institution are conducted using the medications in the RSI kit. This is primarily because of logistical reasons because the RSI kits are readily available at the bedside. The primary sedative infusions used after RSI at the institution were propofol and midazolam and the only analgesic infusion used was fentanyl. The treating physicians and nurses were unaware of the study; hence it could not influence their selection or dosing of medications during and after RSI. The study was approved by the Institutional Review Board before data collection.

Patient selection and categorization

Consecutive patients who received RSI in the ED between July 2009 and June 2010 were included. Patients were excluded if they were younger than 18 or older than 89 years of age (Institutional Review Board requirement for upper age limit), did not receive rocuronium or succinylcholine for paralysis, did not receive etomidate for induction, or had missing medical records. The remaining patients were included in the final cohort. Patients were categorized into two groups on the basis of the paralytic that they received (a) rocuronium or (b) succinylcholine.

Data collection and outcome measures

Data collection was performed by three of the investigators (R.M.T., J.D.K., and L.G.G.) on standardized data collection forms. All data were obtained from a combination of a quality improvement RSI database and the patients' medical records. Before data collection, a 1-h training session was held with all of the data collectors and the senior investigator (A.E.P.). During this session, fields within the medical record and quality improvement database were identified from which data were to be collected. This was done to ensure consistency between the data collectors. Each data collector obtained approximately one-third of the patients in the study. After data collection was complete, a fourth investigator (A.E.S.J.) independently collected data from 10% of the patients in

the study. This sample was selected randomly from the overall cohort. The purpose of this double check was to identify fields that were prone to errors during data collection. No such fields were identified.

Variables collected included patient demographics (age, sex, race, weight), indication for intubation, intubation attempts, trauma status, presence of traumatic brain injury or stroke, vital signs and scores (Glasgow Coma Scale, pain score), and ED length of stay. Pertinent medication information was collected. This included analgesics and sedatives used before RSI, during RSI, and after RSI in the ED. As the focus of this study was on drug dosing after intubation, we obtained infusion rates of sedatives (propofol, midazolam) and analgesics (fentanyl) after intubation at time 0 (start of infusion), 30, 60, and 120 min. The primary outcome measure of this study was the infusion rates of these agents at 30 min, which were compared between the rocuronium and the succinylcholine groups. This duration was selected because patients would most likely be under the effect of rocuronium during this time frame. However, we also made comparisons at the other time points.

Data analyses

The final cohort was divided into two groups for baseline and outcome variable comparisons on the basis of the paralytic used: (a) rocuronium or (b) succinylcholine. An a-priori power analysis was carried out using the method by Cohen [12]. To find a medium effect size difference in infusion rates between the two groups [$d = 0.50$; $d = (\text{mean}_A - \text{mean}_B)/\sigma$], using a power of 80% and an α of 0.05, we estimated that 64 patients would be needed in each group. The infusion rates of each agent (propofol, midazolam, and fentanyl) were compared between the two groups at baseline, 30, 60, and 120 min after initiation. An unpaired Student's *t*-test was used to compare continuous variables. Categorical variables were compared between the two groups using the χ^2 -test. Potential confounders that could influence sedative and analgesic infusion rates after RSI were identified *a priori* by the investigators. As there were no previous studies on which to base these confounders, they were chosen on the basis of the clinical experience of the investigators. Potential confounders included age, sex, race, systolic blood pressure, Glasgow Coma Scale, reason for intubation, trauma, stroke, presence of traumatic brain injury, analgesic or sedative use before RSI, and analgesic or sedative use during infusion. Multivariate linear regression analyses were carried out for the following dependent variables: (a) propofol infusion dose at 30 min and (b) fentanyl infusion dose at 30 min. No model was constructed for midazolam, as there were very few patients who received this agent in the overall cohort. Therefore, two models were constructed. A backward stepwise selection process was used for each model and predictor variables were retained in the model if the

P value was less than 0.2. The primary predictor variable of interest was the paralytic used (rocuronium or succinylcholine). The final models were inspected for collinearity of the predictor variables, heteroskedasticity, and normality of the residuals. Statistics were performed using Stata 11 (Stata Corporation, College Station, Texas, USA). The a-priori α level used was 0.05 for all analyses.

Results

Cohort selection

A total of 434 intubations were performed during the study time frame. Of these, 70 patients were younger than 18 or older than 89 years of age, 69 patients did not receive succinylcholine or rocuronium, 40 patients did not receive etomidate, and one patient's medical record could not be retrieved. Therefore, 254 patients were included in the final cohort (rocuronium = 127 and succinylcholine = 127).

Demographics and baseline variables

Demographic data for the rocuronium and succinylcholine groups are shown in Table 1. There was a statistically significant difference in the mean age between the rocuronium and succinylcholine groups (52.3 vs. 47.2 years, respectively, $P = 0.04$). There were no other baseline demographic differences. The indication for intubation, number of intubation attempts, presence of trauma, traumatic brain injury, or stroke was similar between the groups (Table 1). Comparison of initial vital signs showed a slightly higher systolic blood pressure in the rocuronium group (142.7 vs. 132.6 mmHg, $P = 0.027$). There were no other statistically significant differences with respect to vital signs, the Glasgow Coma Scale, or pain score (Table 1). Length of stay in the ED was <1, 1–4, >4 h in 4, 46, and 50% in the rocuronium group and 9, 50, and 41% in the succinylcholine group, respectively ($P = 0.098$). The proportion of patients who died in the ED was 4 and 1% in the rocuronium and succinylcholine groups, respectively ($P = 0.172$).

Medications before rapid sequence intubation

The use of analgesia before RSI occurred in 9 and 10% ($P = 0.668$) of patients in the rocuronium and succinylcholine groups, respectively. Analgesics used were fentanyl ($n = 10$), morphine ($n = 9$), fentanyl and morphine combination ($n = 3$), hydromorphone and fentanyl combination ($n = 1$), and other ($n = 1$). Although all patients received etomidate for induction, some patients did receive additional sedatives before RSI that was administered earlier during the ED stay. This occurred in 19 and 21% ($P = 0.752$) of patients in the rocuronium and succinylcholine groups, respectively. Sedatives used during this period (before RSI but not for induction) were lorazepam ($n = 30$), midazolam ($n = 14$), diazepam ($n = 2$), lorazepam and diazepam combination ($n = 1$), and others ($n = 3$). All patients received etomidate for induction of RSI, and there was no significant difference

Table 1 Demographic and baseline data

Demographics	Rocuronium (N = 127)	Succinylcholine (N = 127)	<i>P</i> value
Age (years) (mean±SD)	52.3±20.5	47.2±18.5	0.040
Sex (male) (%)	69.3	67.7	0.787
Weight (kg) (mean±SD)	78.5±23.0	83.7±28.1	0.130
Race (%)			
White	59.8	61.4	0.329 ^a
Hispanic	27.6	22.0	
Black	3.1	7.9	
Other	4.7	5.5	
Not specified	4.7	3.1	
Indication for intubation (%)			
Airway protection	74.8	63.0	0.239 ^a
Respiratory failure	14.2	18.1	
Patient control	8.7	15.8	
Cardiac arrest	2.3	2.3	
Hypoxia	0	0.8	
Number of intubation attempts (%)			
1	72.4	74.0	0.754 ^a
2	21.3	18.1	
3 or more	6.4	7.9	
Trauma (%)	43.3	51.6	0.187
Traumatic brain injury (%)	30.7	26.0	0.404
Stroke (%)	11.0	5.5	0.111
Vital signs and scores (mean±SD)			
Systolic blood pressure (mmHg)	142.7±35.8	132.6±36.3	0.027
Diastolic blood pressure (mmHg)	87.1±26.6	84.2±28.7	0.407
Heart rate	103.4±29.1	105.1±24.6	0.612
Respiratory rate	20.9±8.2	22.1±8.4	0.264
Temperature	36.4±1.7	36.3±0.9	0.524
Oxygen saturation (%)			
<95	28.0	26.2	0.747
≥95	72.0	73.8	
Glasgow Coma Scale (%)			
3–8	48.0	35.4	0.113 ^a
9–12	15.7	17.3	
13–15	36.2	47.2	
Pain score (%) ($n = 59$)			
<8/10	46.1	39.4	0.602
≥8/10	53.9	60.6	

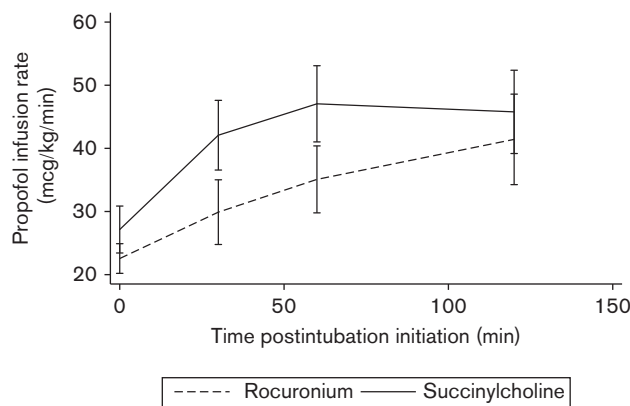
^aOverall *P* value.

in the dosing of etomidate between the rocuronium and succinylcholine groups (0.27 ± 0.09 vs. 0.26 ± 0.09 mg/kg, respectively, $P = 0.243$). The mean dose of rocuronium used was 1.16 ± 0.35 mg/kg and the mean dose of succinylcholine used was 1.49 ± 0.54 mg/kg.

Medications after rapid sequence intubation

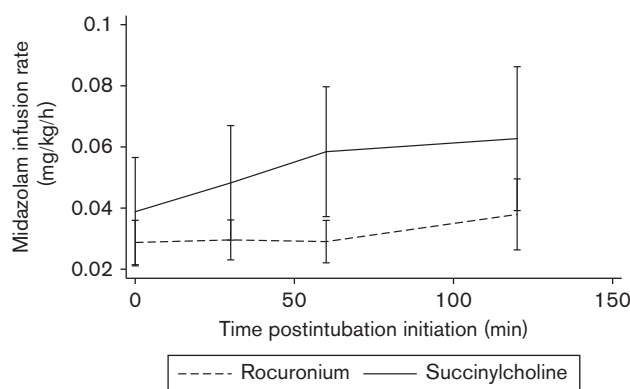
In the overall cohort, 86% ($n = 218$) of patients were administered a sedative infusion and 4% ($n = 11$) were administered sedative boluses but no infusion after RSI during their stay in the ED. The only sedative infusions used were propofol ($n = 169$) and midazolam ($n = 49$). The unadjusted comparisons of sedative infusion dosing at 0, 30, 60, and 120 min after initiation are shown in Figs 1 and 2. The mean propofol infusion rate at 30 min was 30 ± 23 mcg/kg/min in the rocuronium group and 42 ± 24 mcg/kg/min in the succinylcholine group ($P = 0.002$). The mean midazolam infusion rate at 30 min was 0.030 ± 0.014 mg/kg/h in the rocuronium group and 0.048 ± 0.041 mg/kg/h in the succinylcholine group ($P = 0.057$). The median time from RSI to initiation of sedation was 8 min [interquartile range (IQR) 5–15 min] in the succinylcholine group and 12 min (IQR

Fig. 1



Propofol infusion rate after intubation.

Fig. 2



Midazolam infusion rate after intubation.

7–27 min) in the rocuronium group ($P < 0.001$). In the multivariate analyses (Model 1), rocuronium use was associated with lower infusion rates of propofol at 30 min (Table 2). Of the patients who received postintubation sedation infusion ($n = 218$), the rocuronium group was also significantly less likely to receive at least one sedative bolus dose compared with the succinylcholine group (40.1 vs. 66.7%, $P < 0.001$).

A total of 42.5% ($n = 108$) received an analgesic infusion (all patients received fentanyl). An additional 14.2% ($n = 36$) received analgesic boluses but no infusion after RSI. Infusion rates at 0, 30, 60, and 120 min after initiation are shown in Fig. 3. The mean fentanyl infusion rate at 30 min was 0.645 ± 0.545 mcg/kg/h in the rocuronium group and 0.859 ± 0.488 mcg/kg/h in the succinylcholine group ($P = 0.041$). The median time from RSI to initiation of analgesia was 14.5 min (IQR 4–41 min) in the succinylcholine group and 35.5 min

(IQR 12–91 min) in the rocuronium group ($P = 0.002$). In the multivariate analysis (Model 2), rocuronium use was associated with lower infusion rates of fentanyl at 30 min (Table 2). Of patients who received an analgesic infusion ($n = 108$), there was no significant difference between the rocuronium and succinylcholine groups with respect to receiving an additional analgesic bolus during the postintubation ED stay in the rocuronium group compared with the succinylcholine group (44.4 vs. 48.1%, respectively, $P = 0.700$).

There were 39 patients in the study cohort who received a long-acting paralytic after RSI. Most of these patients ($n = 31$) were initially intubated using succinylcholine. All of these patients received rocuronium or vecuronium as the postintubation paralytic after succinylcholine. The median time between succinylcholine use and postintubation paralytic use was 18 min (IQR 7–28).

Adverse effects

A total of 32.2 and 43.7% of patients had hypotension (systolic blood pressure < 90 mmHg) after intubation in the rocuronium and succinylcholine groups, respectively ($P = 0.062$). The mean systolic blood pressure in these patients was 86.4 ± 26.8 and 87.5 ± 19.0 mmHg, respectively ($P = 0.827$). Of these patients ($n = 96$), 29.4 and 22.6% in the rocuronium and succinylcholine groups had their sedative infusion interrupted because of hypotension ($P = 0.478$). Also, 78 and 69% received fluid boluses ($P = 0.329$), and 26.8 and 25.5% were initiated on vasopressors ($P = 0.879$). No other drug-induced adverse effects were identified.

Discussion

A previous study showed that postintubation sedative initiation was delayed after RSI with rocuronium [4]. In this study, we build upon this finding by showing that even after sedatives and analgesics are initiated, the doses used are lower in these patients when compared with patients who received succinylcholine. The lower dosing is sustained for a prolonged period after intubation, which reflects the duration of action of rocuronium, during which the degree of sedation is difficult to assess. Conversely, patients who received succinylcholine received symptom-triggered therapy promptly after intubation. The fact that patients in the succinylcholine group received higher doses of sedative and analgesics during this critical period shows the possibility that patients who received rocuronium were likely underdosed after intubation. Therefore, while patients are pharmacologically paralyzed, some may experience awareness. As a practice complication of anesthesia, this is considered to be second only to death [13]. In the ICU, it is recommended that sustained pharmacological paralysis should be preceded by optimal use of sedatives and analgesics on the basis of physicians' clinical judgment [14]. A similar approach should be used in the ED as well.

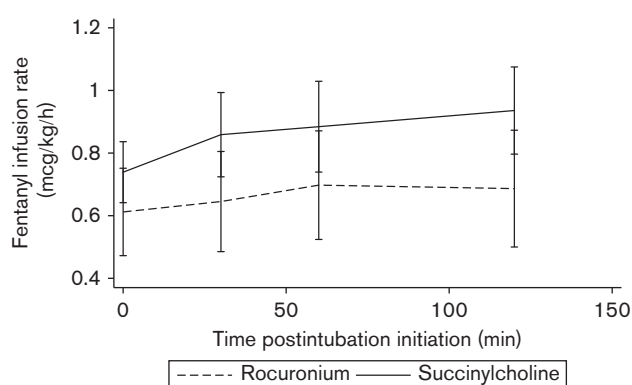
Table 2 Multivariate regression analyses predictive of infusion rates

Variables ^a	Coefficient	95% confidence interval	P value
Model 1: Propofol infusion rate at 30 min in mcg/kg/min ($R^2=0.111$) ($n=143$)			
Paralytic (rocuronium)	-12.165	-20.137 to -4.192	0.003
Trauma	7.215	-2.660 to 17.809	0.151
Traumatic brain injury	-7.390	-17.519 to 2.739	0.151
Postintubation paralytic	-7.607	-18.575 to 3.361	0.172
Age	-0.139	-0.343 to 0.065	0.180
Model 2: Fentanyl infusion rate at 30 min in mcg/kg/h ^b ($R^2=0.432$) ($n=93$)			
Paralytic (rocuronium)	-0.349	-0.570 to -0.128	0.002
Preintubation analgesic	0.403	0.108 to 0.697	0.008
Postintubation sedative	-0.935	-1.69 to -0.176	0.016
Postintubation paralytic	-0.299	-0.642 to 0.043	0.086
Age (years)	-0.005	-0.012 to 0.001	0.092
Trauma	0.178	-0.061 to 0.417	0.143
Systolic blood pressure (mmHg)	0.003	-0.001 to 0.006	0.106

RSI, rapid sequence intubation.

^aPredictor variables added to each model: paralytic, age, sex, race, Glasgow Coma Scale, systolic blood pressure, reason for intubation, trauma, traumatic brain injury, stroke, pre-RSI analgesic, pre-RSI sedative, post-RSI paralytic, post-RSI analgesic (propofol model), post-RSI sedative (fentanyl model), time from RSI to postintubation sedation (propofol model), and time from RSI to postintubation analgesia (fentanyl model). Backward stepwise selection method used with variables retained in each model if $P<0.2$.

^bDependent variable was log transformed to correct for heteroskedasticity.

Fig. 3

Fentanyl infusion rate after intubation.

Rocuronium and succinylcholine have considerable differences in their durations of effect, which influences care after intubation. At a dose of 0.6 mg/kg, rocuronium has a clinical duration of effect of ~30 min, but this duration increases to greater than 60 min at a dose of 1.2 mg/kg [5]. The latter dose is recommended for RSI in the ED [2]. Therefore, patients intubated with rocuronium are likely to be paralyzed for this extended duration after intubation. Note that in our study, the mean dose was 1.16 mg/kg. In contrast, the effect of succinylcholine only lasts for 6 min, which is similar to the duration of effect of the most commonly used induction agent, etomidate [6,7]. These pharmacodynamic differences between the two paralytics had a significant effect on the administration of sedatives and analgesics by ED staff. The unadjusted infusion rates of the sedatives and analgesic were consistently lower after intubation while patients remained in the ED. After adjusting for confounders, rocuronium use was significantly associated

with lower infusion rates in the multivariate models. The type of paralytic used also influenced other aspects of sedative and analgesic dosing. For instance, patients intubated with rocuronium were less likely to receive sedative boluses. Bolus doses are usually provided for agitation and for rapid patient control.

This was a retrospective study with limitations inherent in this study design. However, we took several steps to ensure accuracy of the data collected as described in the Methods section. In addition, dosing information is usually accurately documented, which was our primary outcome of interest. Ideally, a prospective study could be carried out in which patients are interviewed to determine recollection of events after intubation. However, given the results of this study, it would not be ethical to underdose patients in a prospective manner. In addition, such a study design would have considerable challenges such as loss of follow-up because of death or disability, the lack of recollection because of brain injury, and delirium that may occur later during the course of hospitalization, leading to recall bias. Therefore, we used the surrogate end point of drug dosing to compare our groups. Our results suggest that patients administered succinylcholine or rocuronium are treated differently after intubation. Theoretically, there should be no difference in sedative or analgesic requirements between these two groups. In this study, no formal sedation assessments (e.g. Richmond Agitation Sedation Scale) were documented. However, these assessments are not valid in patients who are pharmacologically paralyzed. We achieved our target sample size in the propofol group, but not in the fentanyl group. However, we found statistically significant differences in this latter group as well, which excludes the possibility of a type II error. RSI practices may differ between institutions and from country to country. For instance, at our institution, most intubations are performed using etomidate for induction, with the exception of

patients who are septic. Also, rocuronium use is very common at our institution, as we have shown in previous studies [2,4]. We did not have information on the reason for selection of one paralytic over another. Also, it is possible that the age differences between groups could be related to selection bias. However, we adjusted for this difference in our multivariate models and it is unlikely that the dosing of sedatives and analgesics in the immediate postintubation period would be influenced by these variables. There were patients in the study cohort who received long-acting paralytics after intubation, which could affect dosing of sedatives and analgesics. Also, the time to provision of sedation and analgesia postintubation was different between groups, which could have had an effect of subsequent drug titration. However, the differences in duration are unlikely to change our outcomes. We adjusted for these potential confounders in the regression models.

Conclusion

Patients who receive RSI in the ED using rocuronium are likely to receive lower doses of analgesics and sedatives after intubation compared with patients intubated with succinylcholine. Therefore, clinicians managing patients who have received a long-acting paralytic such as rocuronium should be cognizant of the potential for underdosing of sedatives and analgesics and should optimize the use of these medications immediately after RSI. We recommend that higher doses of sedatives and analgesics should be provided empirically while the patient is pharmacologically paralyzed with long-acting neuromuscular blockers.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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