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ORIGINAL ARTICLE

Low-dose dexmedetomidine provides hemodynamics stabilization during emergence and recovery from general anesthesia in patients undergoing carotid endarterectomy: a randomized double-blind, placebo-controlled trial

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Abstract

Purpose Carotid artery stenosis is a major risk factor for ischemic stroke. Carotid endarterectomy protects patients with severe atherosclerotic carotid artery stenosis against stroke. In such patients, arterial blood pressure is often difficult to control and perioperative hemodynamic instability is associated with high morbidity and mortality after carotid endarterectomy. We performed a randomized double-blind placebo-control trial to evaluate the effects of low-dose dexmedetomidine on hemodynamic stability during the emergence and the recovery phases of general anesthesia in patients undergoing carotid endarterectomy.

Methods Forty-seven patients (68–84 years) were randomly assigned to receive either dexmedetomidine (DEX group) or 0.9% saline (control group). Infusion of dexmedetomidine 1.0 μg/kg/hr for 1 h, followed by 0.2 μg/kg/hr or the same dose of saline was started after carotid artery declamping in the DEX and in the control group, respectively. At the end of surgery, nicardipine was used to maintain systolic arterial pressure within 20% of preoperative values. We compared the maximum dose of nicardipine, time to extubation, plasma catecholamine levels, arterial blood gases, the Richmond Agitation Sedation Scales, visual analogue scale (VAS) in the postanesthesia care unit, and adverse events within 30-days between the control and Dex groups.

Results The baseline clinical characteristics were similar in the two groups. The maximum dose of nicardipine ($p=0.021$), plasma norepinephrine level ($p=0.033$), sedation score and VAS were significantly lower in the Dex group than the control group. There were no differences between the two groups regarding time to extubation, arterial blood gases, and adverse events.

Conclusions Low-dose dexmedetomidine improves hemodynamic stability during emergence and recovery from general anesthesia in patients receiving carotid endarterectomy.

Trial registry number UMIN000010607.

Keywords Dexmedetomidine · Carotid endarterectomy · Hemodynamics

Introduction

Carotid artery stenosis is a major risk factor for ischemic stroke. Carotid endarterectomy has become a standard procedure to protect patients with severe atherosclerotic carotid artery stenosis against stroke [1]. There is no ideal anesthetic regimen for carotid endarterectomy, though general anesthesia is preferred as it provides better surgical conditions and enhances cerebral protection [2]. Perioperative hemodynamic instability is associated with increased morbidity and mortality after carotid endarterectomy [2] and arterial blood pressure is often difficult to control especially during the emergence and the recovery phases of general anesthesia in such patients. High-dose antihypertensive drugs are often needed during carotid endarterectomy to control

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arterial blood pressure but they increase the risk of cerebral hyperperfusion due to vasodilatation.

Dexmedetomidine is a highly selective α_2-adrenoceptor agonist and eight times more specific than clonidine [3]. Dexmedetomidine has hypnotic, sedative, anxiolytic and analgesic properties, and in addition has no significant respiratory depressive effect. Its sympatholytic actions include reduction of mean arterial blood pressure (MAP) and heart rate (HR) through the suppression of norepinephrine release [4–6]. In addition, it can also reduce both the anesthetic and opioid analgesic requirements during the perioperative period. Actually, dexmedetomidine provided reliable and titratable sedation when used for sedation during carotid endarterectomy under regional anesthesia [7, 8]. Alternative sedation techniques using the combinations of propofol, benzodiazepines, and opioids are difficult to titrate and may induce respiratory depression and hypercapnia, which can subsequently increase cerebral perfusion [7].

In this prospective randomized, double-blind, placebo-controlled clinical trial, we tested the hypothesis that dexmedetomidine is effective in hemodynamic stabilization during emergence and recovery from general anesthesia and hence improves the clinical outcome of patients undergoing carotid endarterectomy by stabilizing hemodynamics.

Materials and methods

Subjects

After obtaining approval from the Yao Tokushukai General Hospital Ethics Review Committee (Registered number 24–3; July 2012) and written informed consent from the patients, we studied 50 patients with ASA physical status II or III who were scheduled for elective carotid endarterectomy between April 2013 and April 2015 (Fig. 1). This investigation was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN000010607). Patients were excluded if they had: (1) an allergy to α_2 adrenergic agonist, (2) heart block greater than first degree, (3) history of alcohol or drug abuse, (4) clinically significant renal, hepatic or gastrointestinal disease, (5) received an opioid analgesic medication within 24 h period before the operation, and (6) were pregnant or breast feeding.

Study protocol

In this randomized, double-blind, placebo-controlled clinical trial, the 50 patients were randomly assigned using sealed envelopes to one of the following two treatment groups: (1) the control group received saline, while the (2) Dex group received dexmedetomidine (Fig. 1). The study medications were prepared by the operating room pharmacist in identical 50-ml syringes. Dexmedetomidine 0 or 200 μg was added to saline to achieve a total volume of 50 ml [concentrations: 0 μg/ml (control), and 4 μg/ml (Dex)]. The weight-adjusted doses of all study medications were based on the patient's actual body weight. The investigators, attending anesthesiologists, operating room pharmacist, the postanesthesia care unit (PACU) nurses, as well as the patients were blinded to the group assignment.

Routine perioperative monitoring, including invasive arterial blood pressure, was applied in all patients. Cerebral regional oxygen saturation (rSO_2) was measured using the INVOS 5100B monitor (Somanetics Corporation, Troy, MI). Optrodes were placed on both sides of the patient's forehead immediately above the eyebrow before the induction of anesthesia. A drop in rSO2 of 20% was considered an indicator of cerebral ischemia. None of the patients was premedicated. After administration of O_2, anesthesia was induced using propofol (1–2 mg/kg)

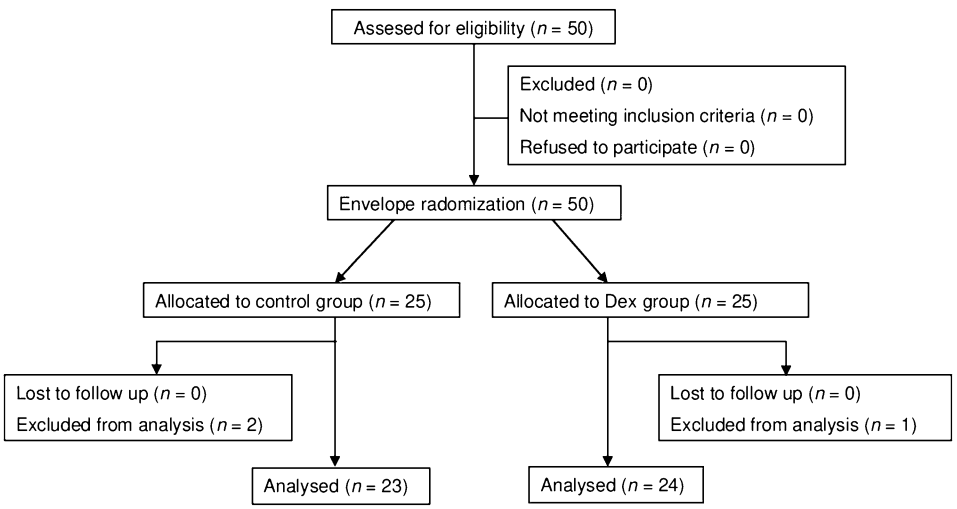

Fig. 1 Flow chart of patient recruitment and randomization. Patients' enrollment was conducted after registration at the University Hospital Medical Information Network Clinical Trials Registry (UMIN000010607). The 50 patients were randomly allocated into the control group or the DEX group. Three patients were excluded from data analysis: 2 because of hemodynamic instability and 1 because of a problem with the INVOS monitor. Finally, 47 patients were analyzed in this study

and remifentanil (0.5 μg/kg/min). Rocuronium was used for initiation and maintenance of muscle relaxation. The trachea was intubated, and the lungs were ventilated for maintaining end-tidal carbon dioxide tension between 30 and 40 mmHg. After the induction of anesthesia, anesthesia was maintained with sevoflurane (1.0–2.0%), O_2, air, and remifentanil through continuous infusion (0.25 μg/kg/min). Bradycardia (HR < 50 bpm) and hypotension (MAP < 20% of baseline) were treated with supplemental doses of atropine (0.5 mg) and phenylephrine (50–100 μg), respectively. Hypertension (MAP > 20% of control) was treated with nicardipine (0.5–1.0 mg).

All surgical procedures in this study were performed using carotid shunting. After an internal shunt was placed from the common carotid artery to the internal carotid artery, the surgeon started dissection of the plaque under a microscope. After carotid artery unclamping, dexmedetomidine (loading, 1.0 μg/kg/h over 60 min; maintenance, 0.2 μg/kg/h) was administered in the Dex group, or equivalent saline in the control group. At the start of wound closure, patients were administered a bolus dose of flurbiprofen axetil 50 mg IV to control acute pain in the early postoperative period. On completion of wound closure, sevoflurane and remifentanil were discontinued and the inspired oxygen flow rate was increased to 5 l/min. The time from discontinuation of sevoflurane to tracheal extubation was recorded. The criteria for extubation required that the patient was able to breathe spontaneously without apnea, arousable on calling. Nicardipine was used to maintain systolic arterial pressure within 20% of preoperative values according to previous review [2]. Nicardipine infusion was initiated at 2.0 μg/kg/min followed by bolus injection (10 μg/kg) over 20% of preoperative values. When systolic arterial pressure increased above 20% of preoperative values for more than 1 min, nicardipine was increased by 1.0 μg/kg/min followed by bolus injection (10 μg/kg). On the other hand, falls in systolic arterial pressure to less than 20% of preoperative values were treated with reduction in nicardipine infusion by 1.0 μg/kg/min. Blood samples taken at 5 min after extubation were collected in tubes with EDTA preservative and centrifuged at 1500 × *g*, at 4 °C, for 10 min. The plasma was aliquoted and stored at − 80 °C until analysis. Plasma catecholamine concentrations were assayed by 3-CAT Research ELISA Kit (IWAKI Co. Ltd., Tokyo, Japan). All assays were performed according to manufacturer's instructions.

After arrival in the PACU, all patients received mask oxygen supplementation (5 l/min) and vital parameters such as invasive blood pressure, HR and pulse oximetry were continuously monitored. Arterial blood gases were analyzed at 1 h after arrival to the PACU to assess respiratory depression. We administered dexmedetomidine, saline and nicardipine for 180 min after arrival in the PACU. If hemodynamic instability persisted 5 min after administration of the randomized medication, the medication was discontinued and this patient was excluded from analysis.

The presence and severity of pain was assessed by an investigator blinded to group allocation using a visual analogue scale (VAS). All patients were asked to score their pain at rest every hour for the first 180 min after arrival in the PACU. The postoperative analgesic regimen consisted of intravenous 50 mg flurbiprofen axetil as required. Sedation score was assessed with the Richmond Agitation Sedation Scale (RASS) (+ 4 = combative, + 3 = very agitated, + 2 = agitated, + 1 = restless, 0 = alert and calm, − 1 = drowsy, − 2 = light sedation, − 3 = moderate sedation, − 4 = deep sedation, − 5 = not arousable) at the same time point. Patients were also assessed for cardiac events by clinical history and 12-lead electrocardiography at 24 h. Neurological events (transient ischemic attack, cerebrovascular accident) or diagnosis of myocardial infarction (made by surgical unit) were recorded up to 30 days. Intraoperative and PACU data were recorded by blinded operating room nurses not associated with the study, and the postoperative clinical assessments were made by the two authors of the study who were blinded as to treatment group allocation.

Data and statistical analyses

The primary outcome measure of this study was the maximum dose of nicardipine. The secondary outcome measures included the total dose of nicardipine for 180 min, time to extubation, plasma catecholamine levels, sedation scores, VAS scores, arterial blood gas analysis and adverse events.

The sample size calculation was based on data from a pilot study that 10 patients (7 males, mean age 71 ± 3) undergoing carotid endarterectomy needed 7.5 μg/kg/min nicardipine infusion and that dexmedetomidine would reduce the nicardipine use. Accordingly, we considered that a clinically significant difference in the maximum dose of nicardipine would be two-thirds reduction with a SD of 2.8 μg/kg/min in the DEX group compared with the control group. A calculation based on $\alpha = 0.05$ and a power of 80% yielded a sample size of 22 patients per group using a two-tailed test. To minimize any effect of data loss, we recruited 50 patients into the study. Continuous data were reported as mean ± SD and analyzed by the Student's *t* test. Categorical data were reported as numbers and percentages and analyzed by the Chi-square or Fisher's exact test, as appropriate. Nonparametric data were reported as median and range, and analyzed by the Mann–Whitney *U* test. The data were tested for normality using the Shapiro–Wilk test. All analyses were performed using SigmaPlot (Systat Software Inc., San Jose, CA, USA). Differences with a *P* value of less than 0.05 were considered statistically significant.

Table 1 Patients' baseline characteristics

	Control ($n=23$)	Dex ($n=24$)	p value
Age (years)	70 ± 6	71 ± 8	0.78
Gender (male/female)	18/5	17/7	0.55
Height (cm)	161.2 ± 9.6	161.2 ± 10.3	0.98
Weight (kg)	61.2 ± 10.3	61.5 ± 10.3	0.94
Duration of surgery (min)	207 ± 46	215 ± 30	0.09
Duration of anesthesia (min)	260 ± 47	266 ± 31	0.14
Total infusion (ml)	1253 ± 134	1322 ± 144	0.10
Urine output (ml)	520 ± 124	490 ± 115	0.39
Blood loss (ml)	95.2 ± 43.1	87.3 ± 33.2	0.47
Coexisting diseases			
Diabetes	10	5	0.09
IHD	6	8	0.58
TIA/stroke	17	15	0.40
Hypertension	20	18	0.29
Medications			
ACEI/ARB	12	16	0.31
Beta-adrenergic blockers	4	4	0.94
Calcium channel blockers	10	14	0.30
Diuretics	1	0	0.30
Baseline systolic blood pressure (mmHg)			
Degree of symptomatic carotid stenosis			
50–69%	4	3	0.63
70–99%	13	12	0.65
Degree of contralateral stenosis			
< 50%	18	20	0.65
50–69%	5	2	0.19
70–99%	0	2	0.15

Values are presented as the mean ± SD or absolute numbers of patients

ACEI angiotensin converting enzyme inhibitors, *ARB* angiotensin receptor blockers, *IHD* ischemic heart disease, *TIA* transient ischemic attack

Results

Data of 2 patients from the control group and 1 patient from the Dex group were excluded from analysis due to missing data. Thus, the final analysis was based on data of 47 patients. There were no significant differences in demographic data between the groups (Table 1).

The maximum doses and total dose for 180 min of nicardipine ($p < 0.05$) and plasma norepinephrine levels ($p = 0.033$) were significantly lower in the Dex group compared with the saline group after extubation, but plasma epinephrine and dopamine levels were similar (Table 2; Fig. 2).

There were significant differences between the median sedation scores at each time point in the PACU after surgery (Table 3). Postoperative VAS pain scores at rest were reduced at all time points assessed in Dex group (Table 3).

Table 2 Nicardipine dose

	Control ($n=23$)	Dex ($n=24$)	p value
Maximun dose (μg/kg/min)	4.6 ± 2.5	2.1 ± 1.5	0.021
Total dose for 180 min (μg/kg)	1254.3 ± 543.2	415.3 ± 215.5	0.013

Values are presented as the mean ± SD

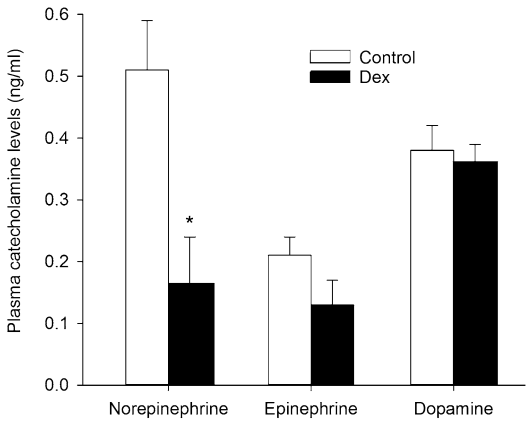

Fig. 2 Effects of normal saline and dexmedetomidine on plasma catecholamine concentrations after tracheal extubation. Plasma norepinephrine concentration was significantly lower in the Dex group than the control group. There was no significant difference in plasma epinephrine and dopamine concentrations between two groups. *$p < 0.05$ versus the control group

Table 3 Time to extubation, postoperative VAS, RAAS and ABG

	Control ($n=23$)	Dex ($n=24$)	p value
Time to extubation (min)	14.8 ± 4.5	16.9 ± 4.5	0.32
Postoperative VAS			
0 h	4.2(3.5–5.2)	2.1 (1.5–3.2)	< 0.001
1 h	4.1 (2.5–5.3)	2.3 (1.0–3.0)	< 0.001
3 h	4.3 (3.2–5.4)	2.2 (1.0–3.0)	< 0.001
Postoperative RASS			
0 h	0 (0–3)	0 (–2–0)	0.03
1 h	0 (0–3)	0 (–2–0)	0.03
3 h	0 (0–3)	0 (–2–0)	0.03
1 h Postoperative ABG			
PaO_2	156 ± 43	152 ± 39	0.82
$PaCO_2$	39.5 ± 3.2	40.7 ± 3.2	0.40

Data are presented as mean ± SD, median (range) and an absolute number of patients

$P < 0.05$ versus control

RASS Richmond Agitation Sedation Scale, *VAS* visual analogue scale, *ABG* arterial blood gas

PaO_2: partial pressure of arterial oxygen, *$PaCO_2$*: partial pressure of arterial carbon dioxide

No falls in cerebral rSO2 exceeding 20% (relative to baseline) were recorded at specific end-points (e.g., induction of anesthesia, 5 min after tracheal intubation, skin incision, time of administration of study drug, 30 and 60 min after administration, tracheal extubation, 5 min after tracheal extubation) in both groups.

Table 4 lists the adverse effects encountered in the two study groups. During surgery, 1 patient of the control group and 4 patients of the Dex group experienced bradycardia, and one and two required one dose of atropine, respectively. Systolic arterial pressure increased by 20% from pre-infusion values during administration of loading dose and was reported as an adverse effect in 1 of 23 patients of the control group and 3 of 24 patients of the Dex group. Systolic arterial pressure decreased by 20% from pre-infusion values during administration of loading dose in 2 of 23 patients of the control group. None of the patients was withdrawn from the study due to these side effects.

Three and two patients developed ipsilateral facial nerve paralysis, as a result of the surgical procedures, from the control and Dex groups, respectively. One patient from the control group developed ipsilateral headache and vomiting but both symptoms resolved spontaneously. No deaths, stroke or myocardial infarction were recorded within 30 days of the study. One patient from the Dex group developed asymptomatic carotid artery stenosis after operation.

Discussion

The main finding of the present study was that dexmedetomidine, infused intraoperatively under general anesthesia of carotid endarterectomy, stabilized the hemodynamics because of effective analgesia during emergence and recovery from anesthesia. This was evidenced by the need for a lower maximum dose of nicardipine in patients receiving dexmedetomidine without delayed recovery from anesthesia or respiratory depression. These effects presumably reflect the action of dexmedetomidine on the central α_2-adrenoceptors, resulting in suppression of hyperadrenergic response and catecholamine levels to carotid endarterectomy.

Carotid endarterectomy is associated with a high incidence of severe postoperative hypertension (up to 40% and 68%) [9, 10], and strict control of arterial blood pressure improves the outcome by reducing neurological complications and wound complications [11], although is difficult to accomplish. In the review of Stoneham and colleagues [2], the target systolic arterial blood pressure was suggested to be less than 160 mmHg or within 20% of the preoperative value. In the present study, we maintained systolic arterial blood pressure within 20% of preoperative value, a value range based on previous studies [12, 13] and our own experience with cerebral rSO_2 monitoring.

The results showed no significant difference in the overall rate of postoperative complications between the two study groups. However, the difference in hemodynamic stabilization based on the use of low-dose dexmedetomidine was significant. Patients of the Dex group were less likely to require treatment for hypertension.

In the present study, nicardipine, a calcium channel blocker, was used as antihypertensive drug. Theoretically, calcium channel blockers can cause cerebral vasodilatation, increase cerebral blood flow, and impair autoregulation after carotid endarterectomy. However, dihydropyridine calcium channel blockers, including nicardipine, are reported to act mainly peripherally and have no specific effects on cerebral blood flow [14]. Administration of nicardipine produces rapid blood pressure control without causing major adverse events [15]. In addition, nicardipine-treated patients are reported to exhibit less variability in blood pressure and require significantly fewer additional interventions [16]. Actually, we safely used nicardipine for adequate blood pressure control by monitoring of cerebral rSO_2. None of the patients experienced a reduction in rSO_2 of more than 20% from baseline, which is considered the clinical threshold of cerebral ischemia.

Increased sympathetic tone and tachycardia are associated with more frequent myocardial ischemia and infarction due to increased myocardial oxygen requirements and low coronary perfusion [17]. Previous data showed that the sympatholytic effects of dexmedetomidine include slowing the heart rate and reducing circulating catecholamine concentrations [8]. In the present study, low–dose dexmedetomidine decreased norepinephrine plasma concentrations and provided appropriate sedation levels immediately after carotid endarterectomy. Furthermore, decreased sympathetic activity was observed during dexmedetomidine administration,

Table 4 Perioperative complications

	Control ($n=23$)	Dex ($n=24$)	p value
During operation			
Hypotension	2	0	0.14
Hypertension	1	3	0.31
Bradycardia	1	4	0.17
Tachycardia	0	0	
Within 30 days			
Death	0	0	
Stroke	0	0	
Myocardial infarction	0	0	
Hyperperfusion syndrome	0	0	
Ipsilateral facial nerve paralysis	3	2	0.60
Carotid artery stenosis	0	1	0.32

Data are presented as number

which was associated with improved hemodynamic stability. These effects offer special advantages to high risk patients undergoing carotid endarterectomy. In contrast, we had no difference between the two groups in the plasma epinephrine and dopamine concentrations. These findings were consistent with those of others, which showed that dexmedetomidine had minimal to no effect on plasma epinephrine concentration [4]. Previous study reported that activation of the α_2-adrenoceptors could interrupt calcium influx via N-type channels and thereby inhibit neurotransmitter release [18]. This inhibition was specific for norepinephrine release as no effect was seen on the concentration of dopamine.

We used maintenance dose of dexmedetomidine of 0.2 μg/kg/hr based on a previous study concerning carotid endarterectomy under general anesthesia [1], although the initial loading dose (1.0 g/kg) was administered over 60 min for preventing hypertension. Using our protocol, only a few patients developed hypertension and there was no significant difference in arterial blood pressure during the administration of the initial loading dose between the two groups. It was important to determine the infusion rate that would maximize the anesthetic and analgesic effects while minimizing the rate of adverse side effects. There were significant differences between the median sedation scores at each time point in the PACU after surgery but there was no disadvantage with regard to postoperative neurological assessment.

The present study has several limitations. First, dexmedetomidine administration induced greater hemodynamic stability during the perioperative course with low incidence of cardiac and neurological events. However, assessment of the potential effects of dexmedetomidine on these uncommon events would require a much larger sample size. Second, the dose of dexmedetomidine used in the present study was lower compared to previous studies. For example, Tufanoqullari and colleagues [6] used 0.2, 0.4, and 0.8 μg/kg/h dexmedetomidine in laparoscopic bariatric surgery. A dexmedetomidine infusion rate of 0.2 μg/kg/h is recommended to minimize the risk of adverse cardiovascular side effects. Although larger doses of dexmedetomidine may be associated with more analgesic and sedative effects, the smallest effective dose seemed to be appropriate in our patients to minimize the risk of adverse events during and after carotid endarterectomy. Third, dexmedetomidine was administered up to only 3 h in the PACU because the dose used in our protocol provided desired sedation levels in the preliminary study. The effects of long-term and low-dose dexmedetomidine on postoperative mortality and hemodynamic stability may differ from those observed in the present study.

In summary, dexmedetomidine induced greater hemodynamic stability during emergence and recovery from general anesthesia, as documented by the low incidence of hypertension and use of antihypertensive drugs, than placebo. Adverse events were infrequent and not different between the placebo and Dex groups. Further studies of large sample size are required to confirm the beneficial effects of dexmedetomidine on cardiac and neurological outcomes.

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Compliance with ethical standards

Conflict of interest The author(s) declare that they have no conflict of interest.

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