

An evolving anesthetic protocol fosters fast tracking in pediatric cardiac surgery: A comparison of two anesthetic techniques

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ABSTRACT

- Background** : The past two decades have seen rapid development of new surgical techniques for repair as well as palliation of complex congenital heart diseases. For a better patient outcome, minimal postoperative ventilation remains one of the most important endpoints of an effectual perioperative management.
- Aims and Objectives** : The aim of this randomized open-label trial was to compare postoperative extubation time and intensive care unit (ICU) stay when two different anesthetic regimens, comprising of induction with ketamine and low-dose fentanyl versus high-dose fentanyl, are used, in pediatric patients undergoing corrective/palliative surgery.
- Materials and Methods** : Patients with congenital cardiac defects, under 14 years of age undergoing cardiac surgery under cardiopulmonary bypass (CPB) and epidural analgesia, were enrolled into two groups – Group K (ketamine with low-dose fentanyl) and Group F (high-dose fentanyl) – over a period of 10 months, starting from January 2018. The effect of both these drugs on postoperative extubation time and ICU stay was compared using Mann-Whitney U-test.
- Results** : A total of 70 patients were assessed with equal distribution in both the groups. In Group K, 32 of 35 patients were extubated in the operation room, whereas extubation time in Group F was 18.1 ± 11 h. Total ICU stay in Group K and Group F was 45.2 ± 30.1 and 60.1 ± 24.5 h, respectively ($P = 0.02$). Systolic blood pressure was significantly higher in Group K.
- Conclusion** : Ketamine along with low-dose fentanyl, when used for anesthetic induction, in comparison to high-dose fentanyl, reduces postoperative extubation time and ICU stay, in pediatric patients undergoing corrective/palliative surgery under CPB and epidural analgesia for congenital cardiac defects.
- Keywords** : Epidural analgesia, fast tracking, neuraxial block, on-table extubation, pediatric anesthesia, pediatric cardiac surgery

INTRODUCTION

Children with congenital heart diseases, undergoing corrective or palliative cardiac surgery, present with

varying degree of severity in terms of ventricular dysfunction, congestive heart failure, pulmonary

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hypertension, and hypoxemia. The surgical repair may be relatively straightforward or may be extremely complex requiring prolonged cardiopulmonary bypass (CPB) and aortic cross-clamp times. The principle objective of an ideal anesthetic induction and maintenance in children undergoing surgical correction of congenital heart disease is to maintain adequate hemodynamics and to provide for superior myocardial preservation while effectively managing surgical stress response.^[1] What qualities should an “ideal” induction agent have when dealing with these patients? Definitely, the subset itself would define this to a great extent (age, weight, prematurity status, shunt, pulmonary hypertension, and status of myocardial function). Nevertheless, the endpoints would still remain as hemodynamic stability, adequate anesthesia, and minimal postoperative ventilation.

The available options are inhalational or intravenous (IV) induction agents. Inhalational induction, especially with sevoflurane,^[1] has been popular till date as it is tagged with the feasibility of fast-track extubation. However, inhalational agents used at appropriate minimum alveolar concentration values for induction and maintenance come at a cost of hemodynamic compromise in these patients with marginal cardiac reserve.^[2] Among IV agents, ketamine is a well-known and widely accepted drug for this purpose.^[3] In high doses, fentanyl has been used over the years as a single drug, and of late, in combination with dexmedetomidine or midazolam.^[4] High dose of opioids such as fentanyl (50–100 mcg/kg) has been described in the literature to effectively obtund the adverse response to laryngoscopy, endotracheal intubation, and surgical stimulus. To avoid the use of high-dose fentanyl, which incites other adverse sequels, namely myocardial depression, respiratory depression, prolonged ventilation, pulmonary atelectasis, and delayed recovery of gut motility, a regional anesthetic technique, as an additional component, is considered beneficial.

In this randomized, open-label study, we have tried to compare the postoperative extubation time and the duration of intensive care unit (ICU) stay when we use ketamine along with low-dose fentanyl versus high-dose fentanyl as induction agents, in children undergoing surgery for congenital cardiac defects. Epidural analgesia was used perioperatively in both these groups. The principle objective is to ascertain if replacing fentanyl induction with ketamine allows earlier extubation. This study is carried out in children who qualify in the Risk Adjustment for Congenital Heart Surgery (RACHS)-1 score of 3 and below. Patients with higher RACHS scores are still candidates for postoperative ventilation, considering the complexity of surgery and hemodynamic alteration.

MATERIALS AND METHODS

The prospective randomized, open-label study was conducted at a tertiary-level cardiac referral center. It was reviewed and approved by the ethics committee of the institute. Written parental informed consent was obtained from 70 patients younger than 14 years undergoing either repair or palliative procedure for congenital heart defects, from January 2018 over a period of 10 months. Exclusion criteria were the presence of any inotropic or ventilatory support before surgery, certain complex congenital heart diseases (pulmonary venous anomalous connection, complete atrioventricular canal defect, truncus arteriosus, and hypoplastic left heart syndrome), presence of severe pulmonary hypertension, and contraindications to central neuraxial block, namely deranged coagulation and spinal deformity.

Triclofos (50 mg/kg) was administered in the ward orally, 45 min before shifting to the operating room (OR). In preoperative room, intranasal ketamine 7 mg/kg and nasal midazolam 0.4 mg/kg were given 15 min before induction. Once inside the OR, basic monitoring was instituted (electrocardiogram, noninvasive blood pressure (IBP), SpO₂, and nasopharyngeal and rectal temperature probes). The patients were randomized to one of the two induction groups, Group K (ketamine with low-dose fentanyl) and Group F (high-dose fentanyl), by randomly computer-generated chits with the specified group name sealed in an envelope, which was done by an investigator not participating in data collection. However, investigators collecting data could not be blinded to the method of allocation of groups.

Each group was allotted 35 patients. In Group K, induction was done with 2 mg/kg IV ketamine supplemented with 2 µg/kg IV fentanyl, and in Group F, 10 µg/kg IV fentanyl was administered. IV rocuronium, 1 mg/kg, was administered to assist oral tracheal intubation in both the groups. Postintubation, mechanical ventilation was initiated with 50% FiO₂ and 0.2%–1.5% isoflurane. At this stage, every child was placed in the right lateral position, and epidural catheter was inserted in T4 to T6 space. Epidural catheter used was 23 G till 3–4 years of age and 20 G for bigger children. Intraoperative epidural drug administration regime was also different for both the groups. In Group K, epidural solution used was 1 ml/kg bolus of 0.25% bupivacaine and 75 µg/kg morphine administered in two divided doses 30 min apart, before the incision, followed by 0.125% bupivacaine at the rate 0.2 ml/kg/h, throughout the intraoperative period and 0.1 ml/kg/h in the postoperative period in the ICU. In Group F, a single-bolus epidural injection was administered containing 75 µg/kg morphine at the time of epidural catheter placement with no intraoperative infusion. Postoperatively, similar infusion as in Group K, i.e., 0.125% bupivacaine at the

rate 0.1 ml/kg/h, was continued in the ICU. Rest of the protocol was the same for both the groups. IV methyl prednisolone (30 mg/Kg) was given to all patients. Injection dexmedetomidine (0.25 µg/kg/h) was started after induction and was continued throughout the perioperative period.

Once the surgery was commenced, 300 Units/kg IV heparin was administered before placing the patient on CPB and was supplemented if indicated by activated clotting time. Dopamine (5 µg/kg/min) and vasopressin (0.0003 Units/kg/min) were started in all the patients, and the dose was titrated as per the demands of hemodynamic status at that time. Intraoperatively, IV fluids were administered as a bolus of 10ml/kg Ringers^[5] lactate with 2ml/kg 25% dextrose over 30 minutes followed by maintenance rate at 1 ml/kg/h. Milrinone was started with the loading dose 100 µg/kg at the release of aortic cross-clamp and was continued at the dose of 0.75 µg/kg/min thereafter.

After surgery, the patients were assessed for fitness to extubate on the table with the following criteria:

- Hemodynamic stability with minimal inotropic support
- No ongoing inappropriate bleeding
- Adequately rewarmed to $>35^{\circ}\text{C}$ and CPB time <150 min
- The patients were ventilated with a synchronized intermittent mandatory ventilation pressure control and pressure support mode with a trigger set at 1 (moderate sensitivity) after weaning from CPB. Gradual weaning from ventilator was initiated, and on completion of surgery, reversal of neuromuscular junction block was achieved with standard doses of neostigmine and glycopyrrolate. The patients were assessed as appropriate for extubation if the adequate tidal volume of >6 ml/Kg was generated on spontaneous mode with a pressure support of 8 cm of H_2O and respiratory rate appropriate for age and weight was seen
- Any of the following present
 - Gag reflex on suctioning
 - Child opening eyes
 - Appropriate limb movements.

Patients not meeting the extubation criteria were shifted to the ICU and were mechanically ventilated with inotropic support (dopamine and milrinone) till the extubation was deemed safe. Other inotropic and vasopressor agents were used as and when indicated. During postoperative stay in the ICU, rescue sedation of propofol 25–50 µg/kg/min IV was started.

Parameters measured were heart rate (HR), IBP, end-tidal CO_2 , core temperature, blood sugar, urine output, near-infrared spectroscopy (NIRS), time to extubation and reintubation (if any), length of stay in

the ICU, and postoperative bleeding. All these values were measured as baseline, at the time of induction, every 10 min intraoperatively, and postoperatively at hourly intervals for initial 6 h followed by 4 hourly intervals till stay in the ICU. Postoperatively, IV fluids in the ICU were continued at 1 ml/kg/h along with 5% albumin at 1 ml/kg/h for 12 h. Urine output (ml/kg/h) was measured at hourly intervals.

Data were expressed in mean and standard deviation. Independent *t*-test was used to test the comparability of groups, based on age and weight of the patients, and Chi-square test was used to test the homogeneity of gender distribution. Quantitative data with respect to postoperative extubation time and ICU stay were compared between the two groups using Mann-Whitney U-test, while such data pertaining to monitoring parameters were compared between the two groups using Student's *t*-test. $P < 0.05$ was considered as statistically significant.

RESULTS

Seventy children were enrolled in the study and randomized to one of the two induction protocols: ketamine with low-dose fentanyl (Group K) or high-dose fentanyl (Group F). There was no fall out seen due to death or any other reason, and all 35 children in each group could be assessed till the end of the study [Figure 1]. The patient characteristics were similar between both the groups with respect to age, weight, and gender [Table 1]. The final randomization of cardiac defects/palliative surgery into the two groups was also comparable [Table 2].

The study clearly displayed the superiority of Group K regimen with respect to fast-track extubation and postoperative ICU stay. In Group K, 32 of 35 children were extubated on the table in the OR, whereas no child was extubated in the OR in Group F. None of the patients in Group F fulfilled the ventilator parameters for extubation. The mean time period for postoperative extubation in Group F was 18.1 ± 11 h [Figure 2]. The postoperative ICU stay in Group K was 45.2 ± 30.1 h and Group F was 60.1 ± 24.5 h ($P = 0.02$) [Figure 3]. There was no statistically significant difference observed at any of the time points selected, in the monitored parameters such as HR, systolic BP (SBP), diastolic BP, mean BP, SpO_2 and NIRS, except in the postinduction phase, when SBP (mmHg) and HR (per minute) were 96 ± 8.9 and

Table 1: Patient characteristics in the two groups

	Group K	Group F	P
Age (years), mean±SD	3±2.6	2.9±3.1	0.880
Weight (kg), mean±SD	12.4±6	11±7.2	0.411
Male, n (%)	22 (62.9)	19 (54.3)	0.467
CPB time (min), mean±SD	80.6±29.1	83.2±23	0.673

CPB: Cardiopulmonary bypass, SD: Standard deviation

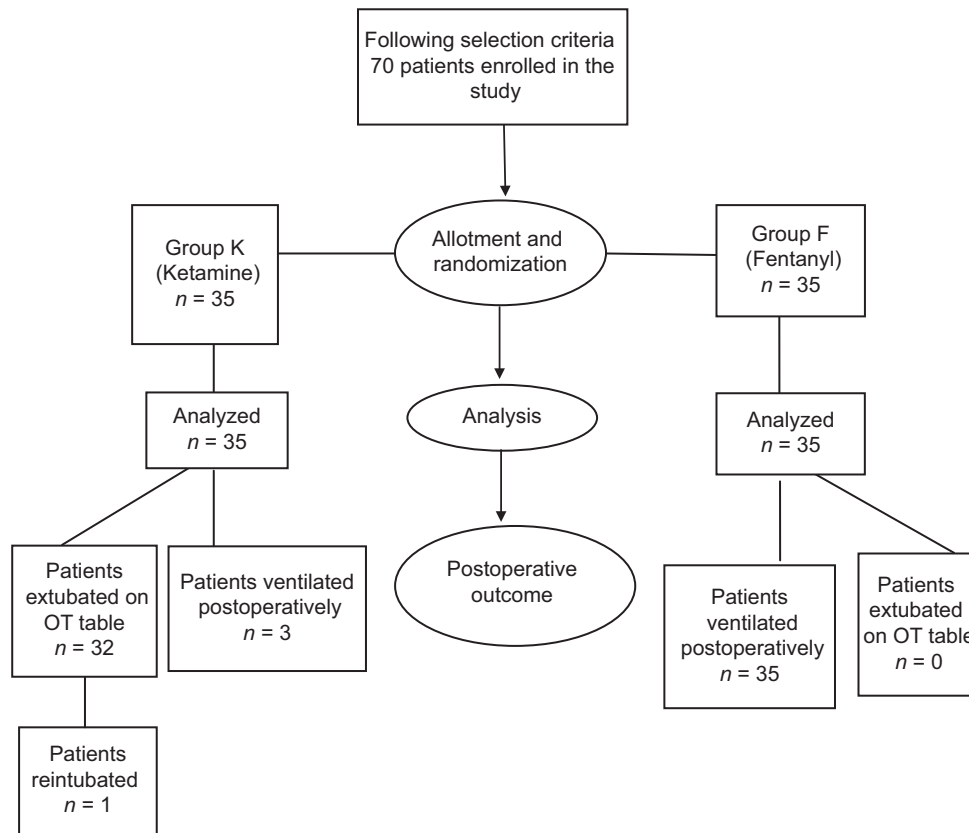


Figure 1: Flowchart outlining the study design and perioperative outcome

Table 2: Distribution of congenital heart diseases into two groups

Cardiac defect/palliative surgery	Group K	Group F
ASD	5	6
VSD	10	9
ASD + VSD	3	4
VSD with PAH	5	4
TOF	5	8
BDG	4	1
Partial AVCD	1	-
Completion Fontan	1	-
Congenital AS	1	-
ASD with cor triatriatum	-	1
Pentalogy of Fallot	-	1
ASD with hypoplastic arch of aorta	-	1

ASD: Atrial septal defect, VSD: Ventricular septal defect, PAH: Pulmonary arterial hypertension, TOF: Tetralogy of Fallot, BDG: Bidirectional Glenn, AVCD: Atrioventricular canal defect, AS: Aortic stenosis

108 ± 10.1 in Group K, whereas 81 ± 12 and 96 ± 11.7 in Group F ($P < 0.01$ for SBP and $P < 0.01$ for HR) [Figure 4].

DISCUSSION

At our institution, the anesthetic protocol for pediatric cardiac surgeries has evolved considerably over the past decade. Earlier, anaesthesia was induced using fentanyl 25–50 µg/kg. This was followed by practice of using fentanyl in the dose of 10 µg/kg along with epidural analgesia at the time of induction. At present, we use ketamine for induction and administer epidural analgesia

at the time of induction, which continues throughout the perioperative period. The primary concern in each of the above protocols was to effectively ameliorate the response to noxious stimuli, thereby preventing an adverse hemodynamic and surgical outcome. In our study, we tried to find a pertinent anesthetic induction regimen, which would truncate the requirement for postoperative ventilation and thereby reduce the hazards associated with it. Until the 1990s, the anesthetic induction, in this group of patients, involved the use of inhalational agents predominantly, as this allowed fast-track extubation, which used to be mandatory in the times when quality ventilators were unavailable. In the ensuing years, with the availability of advanced ventilators with age-appropriate modes, possibility of apparently safe postoperative ventilation broadened the spectrum of anesthetic techniques used for perioperative management. Nevertheless, for over more than a decade now, there has again been a paradigm shift toward early and very early extubation with numerous studies substantiating its feasibility and importance.^[6-12]

Prolonged postoperative ventilation after pediatric cardiac surgery is marred not only by the associated complications^[13-15] but also by the harmful effects of continued sedation and anesthesia in the ICU. Detrimental effects of anesthetic agents with respect to neurodevelopmental outcomes in animals have

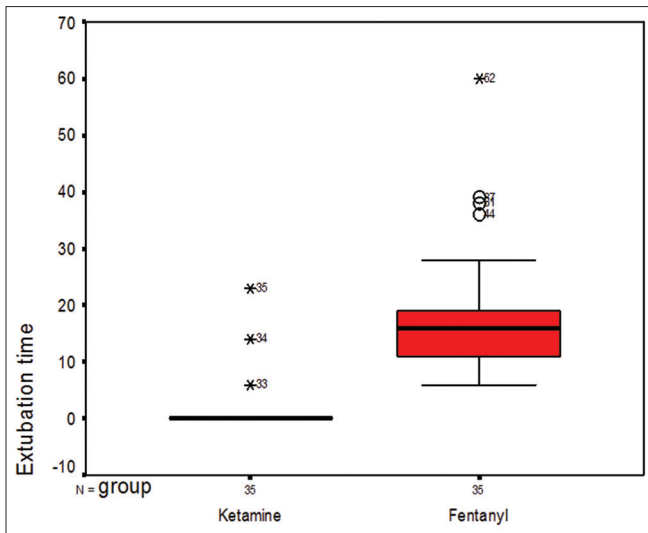


Figure 2: Box plot showing extubation time distribution in two groups (time shown is in hours)

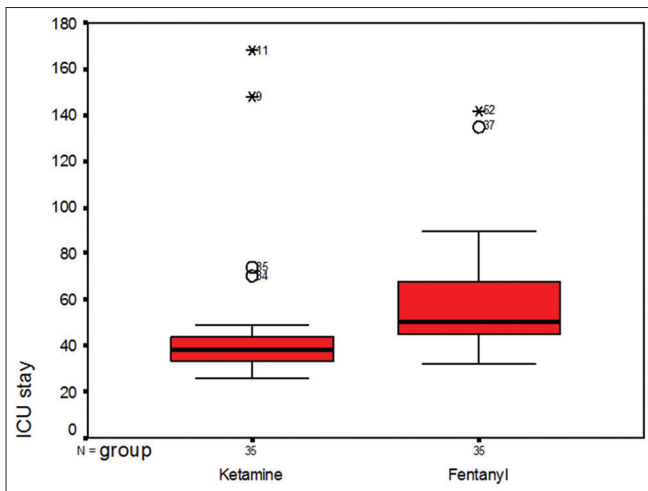


Figure 3: Box plot showing intensive care unit stay time distribution in two groups (time of intensive care unit stay is shown in hours)

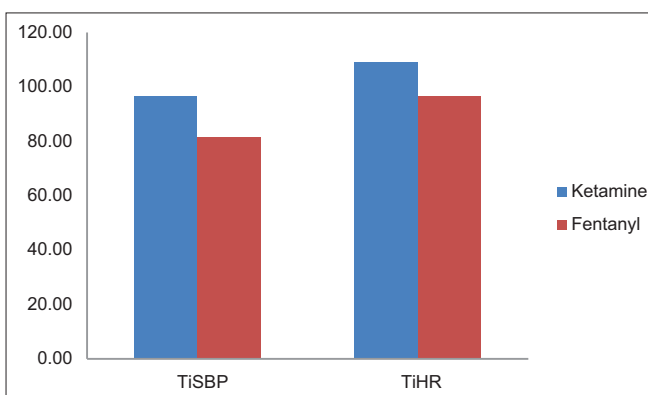


Figure 4: Comparison of systolic blood pressure (SBP) and heart rate (HR) (after anesthetic induction)

been proven.^[16] To add to this, there are additional interventions in the ventilated patients such as central venous and peripheral venous accesses, intra-arterial

catheters, urinary catheters, and, of course, suctioning of endotracheal tube (ETT), which are potential sources of infection. The complications of continued ventilation in the ICU as compared to fast tracking may include accidental extubation, ETT obstruction due to mucus plug or kinking, suctioning-related bleeding or pulmonary hypertensive crisis, laryngotracheal trauma, tracheomalacia, subglottic edema, barotrauma, atelectasis, and ventilator-associated pneumonias.^[17] On the contrary, fast-track extubation may have multiple advantages. It has been known to increase endogenous catecholamines,^[18] thereby enhancing cardiac output, which also gets benefitted by the increased preload, occurring with spontaneous respiration. Overall reduction in the medication and inotropes, which is associated with extubation, reduces the ICU and hospital stay leading to better economics, parental satisfaction, and reduced incidence of nosocomial infections.^[7,19] Finally, early extubation is beneficial in certain cardiac lesions like those with single ventricular physiology^[20] and in certain other defects such as tetralogy of Fallot (TOF) that are prone to right ventricular failure.

Of the various induction agents available, though sevoflurane continues to be popular, with the fast-track extubation tag attached to it, studies have revealed that it is fraught with the perils of hemodynamic disturbances in children with borderline cardiac status.^[1,21] Fentanyl induction, which may be used in as high dose as 20–50 µg/kg, would prevent early extubation. The present study was designed working on the hypothesis that induction with 2 mg/kg ketamine along with low-dose fentanyl supplemented with epidural analgesia would provide for a balanced anesthetic technique while facilitating fast tracking and early extubation in eligible patients.

In this study, we chose to compare ketamine and fentanyl, as neither has significant hemodynamic implications when used for induction. Our target was to formulate a regimen that would minimize postoperative ventilation and ICU stay. Very early extubation or on-table extubation, immediately following congenital heart surgery in a child, warrants the meticulous titration of a balanced anesthetic to ensure adequate anesthesia and analgesia, yet permits sufficient spontaneous respiratory effort. In a study conducted in 2009 by Winch *et al.*,^[22] this balanced anesthetic technique was provided using a volatile agent such as isoflurane and a narcotic such as fentanyl, titrated to effect in doses ranging from 5 to 10 µg/kg. Their study population was <1 year old, and of 391 total patients, 221 could be extubated immediately after the surgery. In our study, this balanced anesthetic technique was provided differently in two groups. In the ketamine group, it was a combination of ketamine, isoflurane, and epidural analgesia, whereas in the fentanyl group, a

combination of fentanyl and isoflurane was used. Of the 35 patients in the ketamine group, 32 could be extubated in the operation room. Among the three patients who did not fulfill the extubation criteria, two were bleeding inappropriately and one was on a high inotropic support post CPB. One child with TOF had to be reintubated after 14 h of ICU stay as he had developed generalized tonic-clonic seizures warranting airway protection. He was subsequently extubated, once stabilized, in another 36 h. In comparison to the ketamine group, no patient from fentanyl group in our study could fulfill extubation criteria. This was in contrast to the study by Winch *et al.* whose extubation rate was almost 55% with the same anesthesia technique. This could probably be explained by two reasons. First, we had administered a bolus of 75 µg/kg epidural morphine at the start of the surgery, in this group. Second, our fentanyl dose was at a higher end of that of Winch *et al.* The synergistic combination could have caused increased sedation and reduced respiratory drive, which was the reason for most of the patients not getting extubated. The protocol, anyways, was devised on the basis of past experience of pediatric cardiothoracic anesthesiologist at our center, with an aim to completely attenuate the surgical stress response. A bigger study, however, may be conducted in future, to compare the two regimens (revised to remove any bias), with respect to parameters such as extubation time, ICU stay, hemodynamic status, inotrope use, and morbidity and mortality.

In our study, dexmedetomidine infusion was also used in both the groups. It is not yet Food and Drug Administration approved for use in pediatric patients, but numerous studies validate its use in the operation room.^[23-26] The increased use of dexmedetomidine for sedation, potentially diminishing respiratory depression, facilitates earlier extubation while maintaining respiratory stability with adequate analgesia following extubation. The extubation criteria that we follow have been substantiated in other studies as well.^[27,28]

CONCLUSION

A combination of ketamine and low-dose fentanyl, when used as an anesthetic induction agent, in comparison to high-dose fentanyl, reduces postoperative extubation time and ICU stay, facilitating a “fast-track” recovery in pediatric patients, undergoing corrective/palliative surgery under CPB and epidural analgesia for congenital cardiac defects. A larger study, in future, may be conducted to compare the two regimens used in this study with respect to parameters such as extubation time, ICU stay, hemodynamic status, inotrope use, cost factors, and morbidity and mortality.

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Conflicts of interest

There are no conflicts of interest.

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