Original Article

Comparison of the effects of dexmedetomidine and nitroglycerin on cerebral oxygen saturation using near-infrared spectroscopy in patients undergoing controlled hypotensive anaesthesia: A randomised controlled non-inferiority trial

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ABSTRACT

Background and Aims: There is limited literature wherein the hypotensive drugs have been compared to know the cerebral effects by monitoring regional cerebral oxygen saturation ($rScO_2$). This study aimed to compare the effects of dexmedetomidine and nitroglycerin on $rScO_2$ during controlled hypotensive anaesthesia using near-infrared spectroscopy (NIRS). The primary objective was to evaluate the non-inferiority of dexmedetomidine versus nitroglycerin in the occurrence of cerebral desaturation events (CDEs) during hypotensive anaesthesia. **Methods:** Adult patients scheduled to undergo head and neck surgery under general anaesthesia randomised to receive either dexmedetomidine or nitroglycerin infusion for controlled hypotensive anaesthesia. Cerebral oximetry was monitored with NIRS, and data regarding CDEs, bilateral $rScO_2$, and peri-operative haemodynamics were collected. Continuous data were analysed using unpaired Student's *t*-tests except for intra-group analyses, which were analysed using paired t-tests. Categorical data were analysed using the Chi-square test. For comparison of time to CDEs, Kaplan–Meier survival analysis with log-rank test was performed. **Results:** Of the 82 patients in both groups, CDEs were observed in 15 patients each. A decrease from baseline by 20% was observed in three patients: one in Group N and two in Group D. Statistically, there was an equal risk of getting CDEs in the groups. The time to CDE was comparable ($P > 0.05$). The difference in heart rate was statistically significant ($P < 0.001$). **Conclusion:** Dexmedetomidine is non-inferior to nitroglycerin in terms of the occurrence of cerebral desaturation events when used for controlled hypotensive anaesthesia in head and neck surgeries.

Keywords: Cerebral desaturation events, dexmedetomidine, hypotensive anaesthesia, near-infrared spectroscopy, nitroglycerin, regional cerebral oxygen saturation

INTRODUCTION

Hypotensive anaesthesia involves achieving a state of hypotension in a deliberate and controlled manner to reduce bleeding and improve the visualisation of the surgical field.[1] Multiple end-points are documented in the literature to achieve hypotensive anaesthesia, such as a decrease in systolic blood pressure to 80–90 mmHg, a decrease in mean arterial pressure (MAP) to 50–65 mmHg in normotensive patients, or

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a 30% decrease in MAP in previously hypertensive patients.[1]

Various pharmacological agents have been studied to find the ideal agent to achieve hypotensive anaesthesia.[2] While the benefits of hypotensive anaesthesia are proven, a word of caution comes along as there is always a risk of hypoperfusion of vital organs.[3] The cerebral, cardiovascular, pulmonary, renal, and hepatic effects of hypotensive anaesthesia have been studied. The cerebral effects deserve specific attention, as monitoring for adequacy of cerebral oxygenation is not a routine practice during anaesthesia. The cerebral effects have been studied by observing postoperative cognitive dysfunction (POCD) as a surrogate indicator of intra-operative cerebral hypoperfusion.[4,5] Cerebral oxygenation can be monitored using jugular venous oximetry, brain tissue partial pressure of oxygen, or near-infrared spectroscopy (NIRS).[6] The NIRS monitors regional cerebral oxygen saturation ($rScO_2$) and gives real-time values in a non-invasive manner. However, there is no defined ischaemic threshold based on the $rScO_2$ values, and there is much variability in the normal baseline values amongst patients. Hence, NIRS is considered a trend monitor where an increase or decrease in values is more important than the absolute value.[7] It is a promising tool for cerebral oximetry and has been used to diagnose cerebral desaturation in major surgeries or surgeries utilising hypotensive anaesthesia.[8] Furthermore, there is limited literature wherein the hypotensive drugs have been compared to know the cerebral effects by monitoring $rScO_2$ using NIRS.

Hence, we hypothesised that dexmedetomidine is non-inferior to nitroglycerin concerning $rScO_2$ in patients undergoing surgery under controlled hypotensive anaesthesia. The primary objective of our study was to compare the occurrence of cerebral desaturation events (CDEs) with dexmedetomidine and nitroglycerin infusions for controlled hypotensive anaesthesia. The secondary objectives were comparing the effects of dexmedetomidine and nitroglycerin on left and right rScO2 and haemodynamics (blood pressure and heart rate).

METHODS

This double-blinded, non-inferiority randomised controlled trial was conducted in a tertiary teaching hospital after approval from the institutional ethics committee (AIIMS/IEC/2018/660 dated 28/09/2018). The trial was registered with the Clinical Trials Registry-India before the recruitment of patients (CTRI/2018/10/016206, dated 30/10/2018; https://ctri.nic.in/). A total of 82 patients of either gender, aged 18–45 years, belonging to American Society of Anesthesiologists (ASA) physical status I and II, and scheduled to undergo head and neck surgery in a supine position with neutral head position, under general anaesthesia with controlled hypotension were enroled. Patients with known, pre-existing cerebral pathology, cognitive disability, carotid artery stenosis, cardiac disease, orthostatic hypotension, and/or sensitivity to study drugs were excluded from the study.

Informed written consent was obtained from the patients for inclusion in the study and for using the data for research and educational purposes. The study was carried out according to the principles of the Declaration of Helsinki (2013) and good clinical practice.

Randomisation was done using computer-generated random numbers to randomise into two groups (groups N and D) to receive nitroglycerin and dexmedetomidine intravenous (IV) infusions to achieve controlled hypotension. Allocation concealment was done with serially numbered opaque sealed envelopes opened by an anaesthesiologist not involved in the study. This person knew only the body weight of the patient and filled two syringes labelled as loading dose and maintenance dose of the study drug. The loading dose syringe of Group N contained 10 mL of normal saline (NS). A maintenance dose of nitroglycerin was prepared by diluting 25 mg (5 mL) with 45 mL NS to a concentration of 500 μg/mL. Loading dose syringe of Group D contained 1 μg/kg of dexmedetomidine diluted in NS in a 10 mL syringe. A maintenance dose of dexmedetomidine was prepared by diluting 200 μg (2 mL) with 48 mL NS to a 4 μg/mL concentration. As the recommended doses of nitroglycerin and dexmedetomidine IV infusion are 0.5–2 μg/kg/min and 0.2–0.7 μg/kg/h, respectively, these concentrations of the study drugs roughly resulted in similar ranges of infusion rates (2.5–12 mL/h in a 50-kg patient) over which they can be titrated for achieving the goal of controlled hypotension, that is, a MAP of 55–65 mmHg. The anaesthesiologist making observations in the perioperative period was unaware of the group allocation as the syringes were labelled as loading dose and maintenance infusion for either of the study drugs.

Patients were fasting per departmental protocol, 6 h for solids and 2 h for clear liquids. Upon arrival in the operating room, appropriate monitors for heart rate (HR), non-invasive blood pressure, peripheral oxygen saturation (SpO_2), bispectral index (BIS), and bilateral $rScO_2$ (NIRS; INVOS 5100c; Medtronic, USA) were attached. Patients were premedicated with IV midazolam 0.03 mg/kg and pre-oxygenated. General anaesthesia was induced with IV fentanyl 2 μg/kg, propofol 2 mg/kg, and rocuronium 0.6 mg/kg, followed by securing an endotracheal tube and mechanical ventilation to target an end-tidal carbon dioxide ($EtCO_2$) of 35–40 mmHg. Maintenance of anaesthesia was done with sevoflurane in an oxygen/air mixture (fraction of inspired oxygen [FiO_2] 0.4) to achieve a BIS value of 45–60. IV 1 μg/kg fentanyl bolus was repeated hourly, and repeat rocuronium boluses were administered to maintain a train-of-four count of 1–-2. The patient's head was maintained in a neutral position throughout.

The arterial cannula was secured and transduced for continuous invasive blood pressure monitoring. Loading dose of the study drug was started when the surgical site was being prepped for surgery, followed by maintenance infusion. The infusion of the study drugs was titrated to achieve MAP in the range of 55–65 mmHg. Continuous monitoring of vitals (HR, invasive MAP, SpO_2, BIS, and bilateral $rScO_2$) was done and recorded before pre-oxygenation and induction (T0); 10 minutes after induction with FiO_2 0.4 (T1) to be considered as baseline value; 10 minutes after starting study drug maintenance infusion (T2); 30, 60, 90, 120 minutes after start of study drug infusion (T3, T4, T5, and T6, respectively); 5 minutes after stopping study drug infusion (T7); and after tracheal extubation when patient was breathing room air (T8). The number of CDEs, with cerebral desaturation defined as 10%, 20%, and 30% reduction in $rScO_2$ from the baseline value (T1) for at least 15 seconds was recorded. The intervention was done when the reduction was over 20% for at least 15 seconds by checking the head position, ventilation (to achieve a $EtCO_2$ of 35–40 mmHg), maintaining MAP within 55–65 mmHg, and increasing FiO_2 and fluid administration. The type and number of interventions were also recorded, as was the time to CDE after administration of the study drugs.

At the end of the surgical procedure, the study drug infusion was stopped, paracetamol 1 g IV was administered, and residual neuromuscular blockade was reversed with IV neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg. After extubation, patients were shifted to the post-anaesthesia care unit (PACU) and then to the ward once the discharge criteria were met.

A study reported that nitroglycerin administration was effective in 95% of cases, resulting in two episodes of CDEs (20% fall from baseline) in 41 patients studied.[9] We planned a non-inferiority trial with a 15% non-inferiority limit. We assumed that there is truly no difference between the nitroglycerin and dexmedetomidine treatment regarding the episode of cerebral desaturation. A minimum of 74 patients were required to prove the non-inferiority of dexmedetomidine at 90% power and a one-sided significance of 5% (95% confidence interval [CI]). Expecting a dropout of 10%, 82 patients were enroled in the study, with 41 patients in each group.

Data were recorded in a Microsoft Excel spreadsheet. Statistical analysis was performed using Statistical Package for Social Sciences version 23 (IBM SPSS Statistics for Windows, Version 23.0, Armonk, NY: IBM Corp, NY, USA). Descriptive statistics were presented in terms of numbers and percentages for categorical variables (gender, CDEs) and in terms of the mean (standard deviation [SD]) and median (interquartile range [IQR]) for the continuous variables (age, weight, height, body mass index (BMI), duration of surgery, time to CDEs, right and left $rScO_2$, and HR). Two independent group variables were compared using the unpaired Student's *t*-test as the criteria for normal distribution were met. Continuous data were analysed using unpaired Student's *t*-tests except for intra-group analyses, which were analysed using paired t-tests. Categorical data were analysed using the Chi-square test. *P* values < 0.05 were considered statistically significant. CIs were calculated for inter-group comparison of primary and secondary objective variables. For comparison of time to CDEs, Kaplan–Meier survival analysis with log-rank test was performed.

RESULTS

Eighty-six patients were assessed for eligibility, of which four refused to participate. Hence, 82 patients were included in the study [Figure 1]. Patients in both groups were comparable concerning age, sex, weight, height, BMI, and duration of surgery [Table 1].

In both groups, CDEs (with a decline of 10% from baseline) were observed in 15 patients each. A decline of 20% (from baseline) was observed in a total of three patients: one in Group N and two in Group D. Statistically, there was an equal risk of getting CDEs (a decline of 10% or 20%) in both groups [Table 2]. None of the patients had a more than 30% decline in baseline values.

Kaplan–Meier survival analysis was done to compare the time to CDE (a decline of 10% from baseline) in the two groups [Figure 2]. In Group N, the mean (95% CI) time to CDEs (by 10%) was 104.64 (94.22–115.06) min, while in Group D, this time was 105.38 (95.44–115.32) min. The time to CDEs was comparable between groups ($P = 0.69$). Kaplan–Meier survival analysis was not performed for time to CDEs by 20% due to a smaller number of patients with a 20% decline from baseline $rScO_2$. Both groups were comparable to each other in terms of right and left $rScO_2$ at all time points ($P > 0.05$) [Figure 3].

The HR was comparable between the two groups at T0 and T1 ($P = 0.721$ and 0.07, respectively). However, from T2 to T8, the difference in the HR in the two groups was statistically significant ($P < 0.001$), and considering the 95% CI, it was more favourable towards group D [Table 3].

DISCUSSION

We observed that nitroglycerin and dexmedetomidine had similar incidences of CDEs and comparable $rScO_2$ values. Nitroglycerin led to tachycardia, while dexmedetomidine caused lower heart rates (both did not require any intervention).

Most studies have compared the effects of various hypotensive agents on blood loss and the quality of the surgical field. In contrast, few have compared the

Table 1: Demographic variables

Parameters	Group N (*n*=41)	Group D (*n*=41)	*P*
Age (years)	26.78 (6.6)	30.05 (8.94)	0.06
Gender (Male/Female)	39/2	36/5	0.24
Weight (kg)	60.15 (7.06)	61.68 (8.55)	0.08
Height (cm)	169.9 (3.49)	169.73 (3.89)	0.83
Body mass index (kg/m^2)	20.75 (1.82)	21.36 (2.69)	0.24
Duration of surgery (min)	124.78 (20.97)	125.61 (35.65)	0.89

Data expressed as mean (standard deviation) or numbers. *n*=Number of patients

Table 2: Cerebral desaturation events (CDEs) by 10% and 20% in the two groups

	CDE by 10%		Odds ratio	95% CI	CDE by 20%		Odds ratio	95% CI
	Yes	No			Yes	No		
Group N (*n*=41)	15	26	1	0.41, 2.46	1	40	2.05	0.18, 23.55
Group D (*n*=41)	15	26			2	39		

n=Number of patients, CI=Confidence interval, CDEs=Cerebral desaturation events

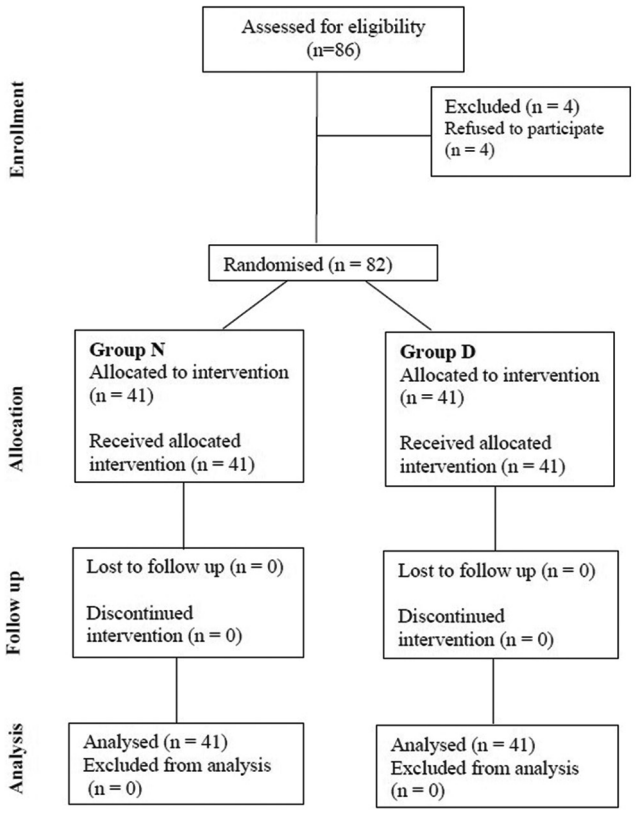

Figure 1: Consolidated Standards of Reporting Trials (CONSORT) diagram

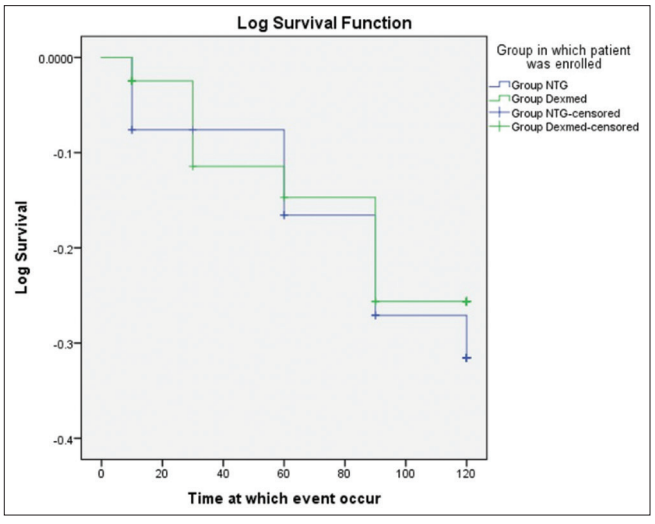

Figure 2: Kaplan–Meier survival analysis for comparison of time to cerebral desaturation event (CDE) between the two groups. NTG = Nitroglycerin; Dexmed = Dexmedetomidine

neurologic impact regarding intra-operative regional cerebral desaturation.[1]

To the best of our knowledge, no studies have compared the neurological implications of hypotensive anaesthesia with dexmedetomidine or nitroglycerin. However, dexmedetomidine has been compared to esmolol, and nitroglycerin has been compared to nicardipine using cerebral oximetry by NIRS.[10,11]

The HR was comparable at T0 and T1 in the two groups. At all other time points (T2–T8), there was a statistically significant difference in HR. The difference observed is because of the effects of the individual drugs. Furthermore, nitroglycerin causes reflex tachycardia, and dexmedetomidine results in bradycardia. With nitroglycerin, HR increased from baseline values 30 minutes after starting its infusion and persisted until after extubation. On the contrary, with dexmedetomidine, HR decreased within 10 minutes of its administration but reached baseline values when the trachea was extubated. Choi *et al*.[10] reported a similar finding of increased HR with nitroglycerin during hypotensive anaesthesia. Maghawry *et al*. observed a decrease in HR on the 'within group' comparison in the dexmedetomidine group.[10,11]

Table 3: Comparison of heart rate between the two groups at different time points

Time point	Heart rate (beats/min)		Mean difference (95% confidence interval)	*P*
	Group N	Group D		
T_0	83.2 (11.1)	82.1 (9.8)	1.0 (−3.9, 5.1)	0.721
T_1	79.9 (8.9)	75.9 (8.8)	4.0 (2.6, 10.5)	0.070
T_2	84.8 (8.5)	70.9 (6.4)	13.9 (11.9, 18.5)	<0.001
T_3	87.4 (9.0)	68.8 (5.9)	18.6 (17.5, 23.8)	<0.001
T_4	88.1 (9.2)	66.9 (5.0)	21.2 (20.3, 26.3)	<0.001
T_5	89.7 (8.4)	65.8 (6.6)	23.9 (22.1, 28.5)	<0.001
T_6	90.3 (6.9)	67.2 (8.8)	23.0 (18.7, 27.4)	<0.001
T_7	89.1 (9.2)	70.5 (10.8)	18.6 (16.6, 24.8)	<0.001
T_8	92.3 (9.5)	76.1 (13.6)	16.1 (12.8, 23.0)	<0.001

Data expressed as mean (standard deviation). T_0: Before pre-oxygenation and induction; T_1:10 minutes after anaesthesia induction (baseline value); T_2: 10 minutes after starting the study drug infusion; T_3, T_4, T_5, T_6: 30,60, 90, 120 minutes after the start of study drug infusion, respectively; T_7: 5 minutes after stopping the study drug infusion; T_8: after extubation, when the patient is breathing, room air

The right and left-sided $rScO_2$ was comparable between the two groups at all the time points ($P > 0.05$). Although we compared the absolute values in the two groups, it is well-known that there is a wide variation in the 'normal values' of $rScO_2$ in the population. Therefore, cerebral oximeters are used as trend monitors, and decisions regarding therapeutic interventions are based on proportional changes rather than absolute values.[12-14]

There is no fixed definition of cerebral desaturation as monitored using NIRS. We recorded CDEs as a 10%, 20%, and 30% decline from baseline $rScO_2$, although we intervened when $rScO_2$ fell by at least 20%. Variable end-points exist as there is no conclusive evidence regarding the extent of fall in $rScO_2$ required to result in cerebral ischaemia. Samra SK *et al*.[15] reported that a 20% or higher fall in $rScO_2$ in the frontal lobes resulted in signs and symptoms of cerebral ischaemia in patients undergoing carotid endarterectomy. On similar lines, Rigamonti *et al*.[16] found that a 20% or more fall in $rScO_2$ was associated with a 20 times increase in apparent signs and symptoms of cerebral ischaemia. Our study found 15 CDEs each in groups N and D, with a 10% fall in $rScO_2$. When a 20% fall was considered, one and two patients had CDE in groups N and D, respectively. In addition, none of the patients in any group had a 30% fall from the baseline. Heller *et al*.[17] reported a reduction in $rScO_2$ by 10% in 62.5% of the 31 patients undergoing functional endoscopic sinus surgery.

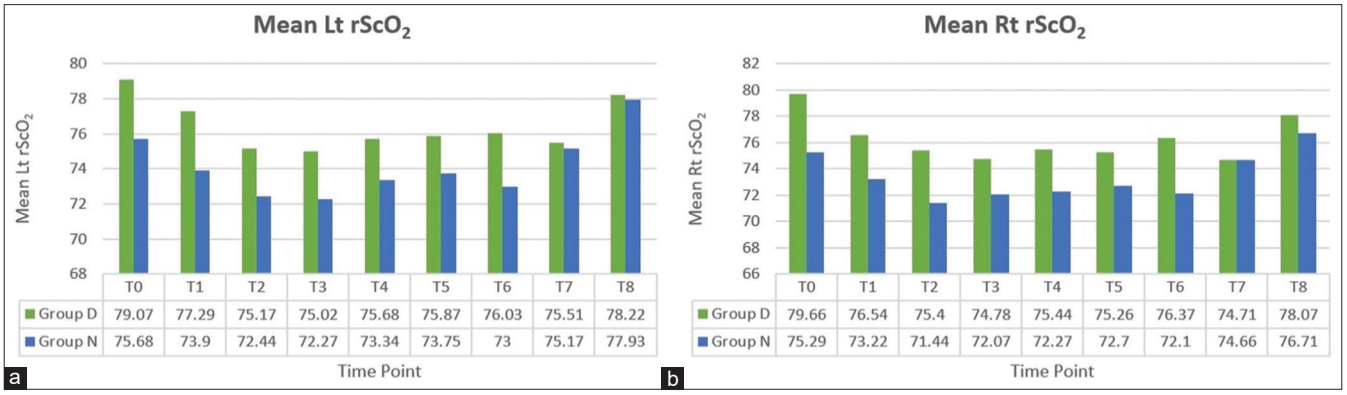

Figure 3: Regional cerebral oxygen saturation in the two groups at different time points: (a) Left-sided, (b) Right-sided. $rScO_2$ = regional cerebral oxygen saturation; Lt = Left-sided; Rt = Right-sided

We intervened when the CDE occurred by at least a 20% fall in $rScO_2$. In one patient each in the nitroglycerin and dexmedetomidine group, $rScO_2$ increased to baseline by turning the head back to a neutral position, which had been inadvertently turned to one side. Another patient in the dexmedetomidine group had the head already in the neutral position, and the $rScO_2$ returned to baseline value by increasing the FiO_2 to 0.5 from 0.4. MAP was above 55 mmHg in all three instances, within our target range for controlled hypotension. There is no universal protocol to manage the decrease in $rScO_2$.[14] However, Denault *et al*.[18] published a treatment algorithm to manage CDEs with more than a 20% decline in $rScO_2$. They recommend checking the head position and endotracheal tube ties first, followed by optimising oxygen delivery (by ensuring adequate cardiac output, MAP, SpO_2, partial pressure of carbon dioxide, and haemoglobin) and oxygen consumption (by providing adequate depth of anaesthesia, normothermia, and by ruling out intra-operative seizure activity).

There are a few limitations in our study. Firstly, we did not compare the primary advantages of controlled hypotensive anaesthesia, such as blood loss, and the quality of surgical field visualisation as high-quality evidence related to these observations is already available. We did not observe the total consumption of nitroglycerin and dexmedetomidine. The postoperative sedation score and length of PACU stay were not observed, which might have been different between the two groups owing to the properties of dexmedetomidine. The POCD data was not captured as the patients were discharged on the first or second postoperative day, and telephonic assessment for cognitive function was not feasible. In addition, the limitations inherent to NIRS might be reflected in our study, such as it gives the regional status of cerebral oximetry and not global.

CONCLUSION

As nitroglycerin and dexmedetomidine had similar incidences of cerebral desaturation events, dexmedetomidine is non-inferior to nitroglycerin when used for controlled hypotensive anaesthesia in head and neck surgeries with the head in a neutral position and lasting less than two hours.

Statement on data sharing

De-identified data may be requested with reasonable justification from the authors (email to the corresponding author) and shall be shared after approval as per the authors' Institution policy.

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Conflicts of interest

There are no conflicts of interest.

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