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ORIGINAL ARTICLE

Effect of acute normovolemic hemodilution in patients undergoing cardiac surgery with remimazolam anesthesia

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Abstract

Purpose The reduced effects of allogeneic transfusion with acute normovolemic hemodilution (ANH) have been reported. Harvesting a large volume of blood may maximize the effect in patients with low body weight, and the prevention of hypotension is important. Remimazolam is an anesthetic with few circulatory responses. Our aim was to evaluate whether high-volume ANH reduces the need for transfusion in cardiac patients under remimazolam anesthesia.

Methods In this retrospective single-center study, we enrolled cardiopulmonary bypass (CPB) patients who received remimazolam anesthesia. Changes in hemodynamic parameters were assessed. The numbers of blood transfusions and chest tube outputs were also evaluated.

Results In a total of 51 patients, ANH was performed in 27 patients with a mean body mass index of 23.2 (ANH volume: 740 ± 222 mL). No significant differences were observed in mean blood pressure during blood collection. The intraoperative amount of red blood cell (RBC) transfusion was significantly lower in the ANH group than in the control group (431 ± 678 and 1260 ± 572 mL, $p < 0.001$). The avoidance rates of RBC were 66.7 and 4.2%, respectively. The multivariate analysis result revealed that ANH correlated with RBC, with an odds ratio of 0.067 (95% confidence interval 0.005–0.84, $p < 0.05$). The postoperative bleeding at 24 h was significantly lower in the ANH group (455 ± 228 and 797 ± 535 mL, $p < 0.01$).

Conclusion In patients undergoing CPB, ANH reduced intraoperative transfusion amount and postoperative bleeding. Hemodynamic changes during blood collection were minimal under remimazolam anesthesia and high-volume ANH was feasible.

Keywords Acute normovolemic hemodilution · Transfusion · Cardiopulmonary bypass · Coagulation · Hemostasis

Introduction

Allogeneic blood transfusions are associated with poor outcomes in cardiac surgery [1, 2]. The effectiveness of acute normovolemic hemodilution (ANH) has been reported in patients undergoing cardiopulmonary bypass (CPB) surgery [3–5]. Meta-analyses showed that ANH reduces allogeneic transfusion amount and blood loss [6], and patient blood management guidelines recommend ANH as part of a multimodal blood conservation strategy for patients undergoing CPB [7]. The ANH is performed less frequently in patients with lower body weight, who have less blood volume [3, 5]. Recent report showed that patients with lower body mass index (BMI) need more allogeneic transfusions in cardiac surgery [8]. Although ANH may provide high reduction effect of blood transfusions in patients with low BMI, but the so-called ‘high-volume ANH’ which collects blood volume of > 12 mL/kg may be challenging [9]. Prevention of hypotension during blood collection is very important to maximize the benefit of ANH.

Benzodiazepine have less cardiovascular depressant responses in cardiac surgery [10]. Remimazolam is a novel ultrashort-acting drug with high affinity for the benzodiazepine-binding site of the γ-aminobutyric acid receptor [11]. It has been reported that remimazolam is associated with less circulatory responses during anesthetic induction in high-risk surgical patients [12–15]. To date, effects of ANH has not been evaluated in patients with remimazolam anesthesia. We hypothesized that high-volume blood collection under stable hemodynamics is enabled in cardiac patients under

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remimazolam anesthesia, and ANH reduces the amount of allogeneic blood transfusions. Therefore, we evaluated changes in hemodynamic and hematological parameters during blood collection in patients undergoing CPB who received remimazolam anesthesia. We also investigated the effects of ANH on blood transfusions and postoperative blood loss.

Methods

Patient population

This retrospective single-center study was conducted with the approval of the Institutional Review Board of the Kyoto Prefectural University of Medicine (# C-2830). Owing to the retrospective nature of the study, the requirement for written informed consent from individual patients was waived. We enrolled all patients undergoing CPB surgery who received total intravenous anesthesia with remimazolam from July 1, 2021 to July 31, 2023. Patients who underwent ANH were defined to the ANH group, and those who did not underwent ANH were defined to the control group. Patients receiving anticoagulation therapy before surgery, those with preexisting hepatic dysfunction, and those scheduled for emergency surgery were excluded. The following variables were collected: age, sex, height, body weight, BMI, type of surgery, European System for Cardiac Operation Risk Evaluation II (EuroSCORE II), American Society of Anesthesiologists-Physical Status (ASA-PS), preoperative hematological variables, blood volume of ANH, and fluid amounts. Changes in mean arterial blood pressure, heart rate, hematocrit, and platelet count before and after induction were also recorded. The primary outcomes were the amount and avoidance of blood transfusions during and after surgery. The avoidance rate of transfusion was defined as the proportion of patients who avoid allogeneic blood transfusion to total number of patients. Chest tube output, duration of mechanical ventilation, intensive care unit (ICU) stay, and hospital mortality were evaluated as secondary outcomes.

Blood management practices

After induction of anesthesia with remimazolam (Anerem; Mundipharma K. K., Tokyo, Japan), the continuous infusion was adjusted between 0.5 and 1.0 mg/kg/h. A total dose of 15–20 µg/kg of fentanyl was administered during surgery. ANH in cardiac surgical patients is an accepted practice at our institution. Following the institutional protocol, the feasibility of ANH was at the discretion of an anesthesiologist. The absolute contraindications for ANH were preoperative hematocrit < 30%, a left ventricular ejection fraction < 35%, or preoperative continuous infusion of inotropes. Whole blood was collected prior to systemic heparinization for CPB. Whole blood was drawn from the introducer of the right internal jugular vein and collected in a 400 mL sterile blood storage bag containing 56 mL of citrate phosphate-dextrose adenine (Terumo, Tokyo, Japan). The total volume of the corrected blood was determined at the discretion of the attending anesthesiologist based on changes in hematocrit, arterial blood pressure, transesophageal echocardiography, and regional cerebral oxygen saturation. For hypotension during blood collection, a bolus dose of a vasopressor was administered as needed. The whole blood was replaced using either crystalloid solution or 6% hydroxyethyl starch, at a 1:1 ratio or less. The blood bags were stored at room temperature (20–24 °C). A 300 IU/kg of heparin was given before instituting CPB. Activated clotting time was maintained above 450 s during CPB (Hemochron Signature Elite; Werfen, San Diego, CA, USA). CPB circuit was primed with approximately 1000–1200 mL of a solution consisting of crystalloid solution, 15% mannitol, and heparin. Ultrafiltration was performed during CPB to remove excess fluid, when feasible. Heparin was reversed with 3 mg/kg protamine sulfate while weaning from CPB, and ANH blood was reinfused into the patient. Red blood cell (RBC) products were transfused to maintain the hematocrit above 20% during CPB and 25% in the ICU. An intraoperative cell-salvage device was used. Plasma and platelet transfusions were performed by a clinical team caring for the patients.

Statistical analysis

All patients were divided into the ANH and control groups. Data are expressed as mean ± standard deviation (SD) or median (interquartile range), as appropriate. The statistical significance of the difference between the two groups was assessed using the nonparametric Mann–Whitney *U* test, Friedman test, or Fisher's exact test, as appropriate. To calculate odds ratios (ORs) and 95% confidence intervals (CI) for assessment of the correlation between allogeneic blood transfusion and ANH, univariate and multivariate logistic regression analyses were conducted. The variables that were significantly different between the two groups in the patient's background were adjusted in the multivariate analysis. A p value of < 0.05 was considered as significant. All analyses were performed using EZR (version 1.61; Saitama Medical Center, Jichi Medical University, Saitama, Japan) or GraphPad Prism (version 9; GraphPad Software Inc., San Diego, CA, USA) [16].

Results

During the study period, we identified a total of 51 patients, and ANH was conducted with 27 patients (52.9%). The demographic data of the study groups are shown in Table 1.

There were significant differences in age and preoperative hematocrit levels; however, no other differences were found between the two groups.

In the ANH group, the mean volume of collected blood was 740 ± 222 mL (12.3 ± 3.6 mL/kg, Table 2). In all cases, blood collections were completed before the start of surgery. No patient required continuous infusion of vasopressors or catecholamines before CPB because of severe hypotension after blood collection. No significant differences in mean arterial blood pressure or heart rate after induction were observed between the two groups (Fig. 1). The hematocrit level decreased after 400 mL of blood collection (after induction: 38.3 ± 3.9%, after collecting 400 mL blood: 34.4 ± 3.9%), but the change was minimal with additional 400 mL collection (Fig. 2A). The hematocrit level at ICU arrival was significantly higher in the ANH group than in the control group (33.7 ± 2.7% and 30.3 ± 3.9%, respectively; $p < 0.01$). There were no differences in the platelet counts at any time point (Fig. 2B). There was no difference in the plasma fibrinogen levels at ICU admission between the two groups (224 ± 50 mg/dL and 232 ± 46 mg/dL, respectively).

Table 1 Demographic and surgical data

Variable	ANH group	Control group	*p* value
n	27	24	
Age (year)	68.9 ± 9.9	74.3 ± 8.5	< 0.05
Female	11 (40.7%)	15 (62.5%)	0.16
Height (cm)	161 ± 7.1	157 ± 9.3	0.11
Weight (kg)	60.6 ± 11	57.3 ± 11	0.17
BMI (kg/m^2)	23.2 ± 3.6	23.1 ± 3.5	0.86
Hypertension	10	12	0.41
Diabetes mellitus	7	2	0.15
Cerebral vascular disease	2	2	1.00
Severe aortic stenosis	12 (44.4%)	8 (33.3%)	0.57
Redo surgery	0	0	1.00
Preoperative anti-platelets	3	3	1.00
Preoperative anti-coagulants	2	2	1.00
Hematocrit (%)	41.8 ± 3.2	36.6 ± 4.1	< 0.001
Platelet count (× 10^3/μL)	219 ± 55	221 ± 135	0.28
PT/INR	1.0 ± 0.1	1.2 ± 0.4	0.50
Fibrinogen (mg/dL)	357 ± 94	340 ± 114	0.58
EuroSCORE II			
Low risk: 0–2 (%)	21 (77.8%)	13 (54.2%)	0.13
Intermediate risk: 3–5 (%)	6 (22.2%)	8 (33.3%)	0.53
High risk: 6– (%)	0 (0.0%)	3 (12.5%)	0.10
ASA-PS: 1/2/3/4	0/2/5/20	0/0/11/13	–
Surgery type			
Isolated valve	14 (51.8%)	8 (33.3%)	0.26
Multiple valve	5 (18.5%)	4 (16.6%)	1.00
Aortic aneurysm	4 (14.8%)	3 (12.5%)	1.00
Isolated CABG	0 (0.0%)	0 (0.0%)	1.00
Combined surgery	4 (14.8%)	9 (37.5%)	0.11
CPB duration (min)	180 ± 57	196 ± 52	0.31
Cross-clamp time (min)	127 ± 48	127 ± 34	0.79
DHCA	7 (25.9%)	9 (37.5%)	0.54
CPB prime volume (mL)	1044 ± 202	954 ± 233	0.16

ANH acute normovolemic hemodilution, *BMI* body mass index, *PT/INR* prothrombin time/international normalized ratio, *EuroSCORE II* European system for cardiac operation risk evaluation II, *ASA-PS* American Society of Anesthesiologists-Physical Status, *CABG* coronary artery bypass graft surgery, *DHCA* deep hypothermic circulatory arrest, *CPB* cardiopulmonary bypass

Table 2 Fluid amounts and non-transfusion related outcomes

	ANH group	Control group	*p* value
Volume of ANH (mL)	740 ± 222	–	–
(mL/kg)	12.3 ± 3.6	–	–
Intraoperative fluid			
Crystalloid (mL)	2167 ± 1998	3459 ± 2047	< 0.01
Albumin (mL)	180 ± 231	273 ± 259	0.1
6% HES (mL)	296 ± 330	96 ± 175	< 0.05
Need for vasopressors or inotropes CIV before CPB	0	0	1.0
Chest drainage volume			
At 12 h (ml)	289 ± 228	535 ± 337	< 0.01
At 24 h (ml)	455 ± 228	797 ± 535	< 0.01
Reoperation for bleeding	0 (0%)	0 (0%)	1.0
Ventilation time (h)	8.8 ± 16	9.1 ± 11	0.72
ICU stay (h)	32.5 ± 32	37.4 ± 22	0.92
Hospital mortality	0 (0%)	0 (0%)	1.0

ANH acute normovolemic hemodilution, *CIV* continuous intravenous, *CPB* cardiopulmonary bypass, *HES* hydroxyethyl starch, *ICU* intensive care unit

The amount of RBC transfused intraoperatively was significantly lower in the ANH group than in the control group (431 ± 678 mL and 1260 ± 572 mL, respectively; $p < 0.001$) (Fig. 3). The intraoperative amounts of all transfusion products were lower in the ANH group (1160 ± 1217 mL and 2737 ± 972 mL, respectively; $p < 0.001$). The avoidance rate of RBC transfusion was 66.7% in the ANH group, while it was 4.2% in the control group ($p < 0.001$). In addition, the intraoperative use of fresh frozen plasma (FFP) was significantly lower in the ANH group, compared to the control group (489 ± 554 mL and 1185 ± 516 mL, respectively; $p < 0.001$). The avoidance rate of FFP was also higher in the ANH group (48.1% and 4.2%, respectively; $p < 0.001$). The results of the multivariate analysis adjusted for age and preoperative hematocrit revealed that ANH correlated with RBC and FFP transfusion, ORs of 0.067 (95% CI 0.005–0.84) for RBC transfusion and 0.064 (0.005–0.89) for FFP transfusion ($p < 0.05$, respectively; Table 3).

The postoperative usage of all transfusion products was lower in the ANH group than in the control

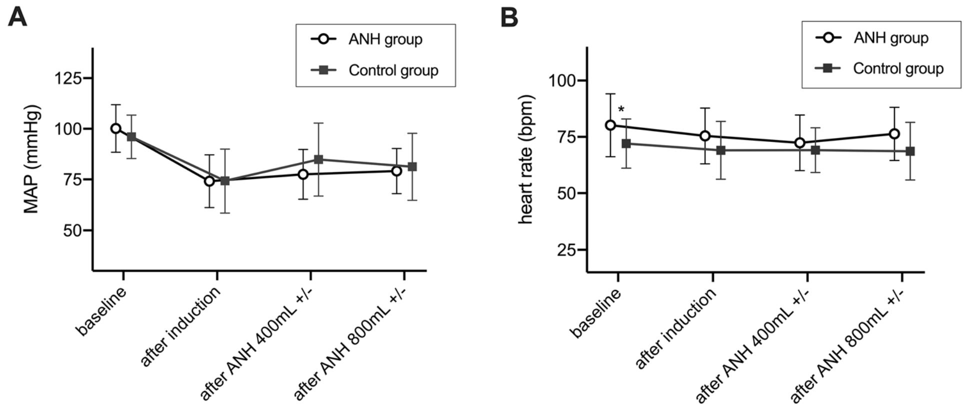

Fig. 1 Hemodynamic change before and after anesthetic induction. Compared to the control group, no significant changes are observed in the hemodynamic parameters during blood collection in the ANH group. $*p<0.05$. *MAP* mean arterial pressure, *ANH* acute normovolemic hemodilution

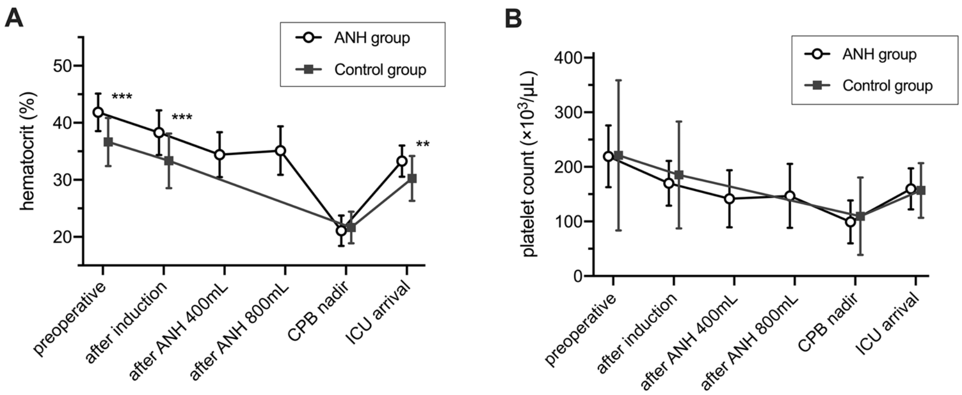

Fig. 2 Trends of hematocrit and platelet count. The hematocrit level decreased after 400 mL of blood is collected, but the change is minimal after additional blood collection. The hematocrit level upon ICU arrival is higher in the ANH group. There are no differences in platelet counts during surgery. $**p<0.01$, $***p<0.001$. *ANH* acute normovolemic hemodilution, *CPB* cardiopulmonary bypass, *ICU* intensive care unit

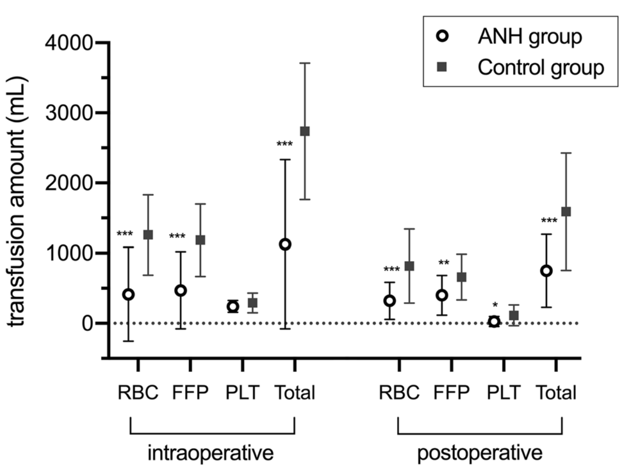

Fig. 3 Intraoperative and postoperative amounts of allogeneic transfusion products. The numbers of RBC and FFP transfused intraoperatively are lower in the ANH group. The total postoperative amount is lower in the ANH group than in the control group. $*p<0.05$, $**p<0.01$, $***p<0.001$. *ANH* acute normovolemic hemodilution, *RBC* red blood cell, *FFP* fresh frozen plasma, *PLT* platelet concentrate

Table 3 Univariate and multivariate analyses of ANH and intraoperative transfusion

	Univariate regression		Multivariate regression	
	Odds ratios (95% CI)	*p* value	Odds ratios (95% CI)	*p* value
RBC	0.022 (0.003–0.18)	< 0.001	0.067 (0.005–0.84)	< 0.05
FFP	0.047 (0.006–0.40)	< 0.01	0.064 (0.005–0.89)	< 0.05
PLT	1.14 (0.15–8.76)	0.90	3.41 (0.16–73.8)	0.43

Adjusted for age, and preoperative hematocrit level

ANH acute normovolemic hemodilution, *CI* confidence interval, *RBC* red blood cell, *FFP* fresh frozen plasma, *PLT* platelet concentrate

group (769 ± 520 mL and 1591 ± 837 mL, respectively; $p<0.001$). The chest tube output at 24 h was significantly lower in the ANH group (455 ± 228 mL and 797 ± 535 mL, respectively; $p<0.01$, Table 2). There were no differences in the duration of mechanical ventilation or ICU stay between the two groups. No hospital mortality was reported in any patient.

Discussion

In a retrospective observational study for patients undergoing CPB with remimazolam anesthesia, the intraoperative use of allogeneic blood transfusions was lower in the ANH group than in the control group. The number of postoperative blood transfusions and blood loss were also lower in the ANH group. Hemodynamic changes during blood collection in the ANH group were minimal under remimazolam anesthesia, and a large volume of blood with a mean of 12.3 mL/kg was obtained in the Asian patient population.

A recent report from 26,499 US patients undergoing cardiac surgery showed that patient group with a BMI below 25 is the highest risk group for allogeneic blood transfusion, and the subgroup included higher ratio of Asians [8]. It is obvious that the ANH is less likely to be performed in patients with lower BMI, and collected blood volume would be relatively lesser even if ANH is performed [3]. While ANH is performed with 17% of cardiac surgery in the US [3], recent study reported that the prevalence in Japan is only 5% [5]. For ANH in patients with low body weight, anesthetic management while preventing hypotension and hemodilution during blood collection may be encouraged. We assumed that high prevalence of ANH with 52.9% in our study was achieved due to stable hemodynamics after the induction under remimazolam anesthesia. Liu et al. have compared the effects of remimazolam ($n=30$, 0.3 mg/kg bolus) and propofol ($n=30$, 2.5 μg/mL of target-controlled infusion) on hemodynamics during the induction in patients undergoing valve replacement surgery [13]. In their study, the frequency of hypotension, defined as a mean arterial blood pressure below 60 mmHg, was significantly lower in the remimazolam group than in the propofol group (16.7% and 43.3%, respectively). The use of norepinephrine for hypotension was lower in the remimazolam group. Similar to midazolam, sympathetic tone and peripheral vascular resistance may be preserved under remimazolam anesthesia.

In a Japanese survey using Diagnosis Procedure Combination database, the proportion of patients with aortic valve stenosis among all ANH cases was only 2.3% (43/1906 patients) [5]. Interestingly, the prevalence of severe aortic valve stenosis in the ANH group was as high as 44.4% in our study. Nevertheless, adequate blood volumes were obtained from the patients. It is presumed that the anesthesiologists tended to use remimazolam as an anesthetic, particularly for high-risk patients who need avoidance of hypotension after induction [12]. The MAP was stable during and after blood collection, and there were no cases requiring continuous infusion of vasopressors prior to CPB. Damen et al. evaluated whether prevention of hypotension during the induction could avoid hemodilution in cardiac patients anesthetized with propofol and sevoflurane [17]. They showed that hematocrit change before and after the induction in the interventional group (continuous infusion of noradrenaline) was lower compared to that in the control group ($1.2 \pm 1.4\%$ and $5.0 \pm 2.5\%$, respectively). In cardiac patients, hemostatic functions are disturbed due to hemodilution [18, 19]. Prevention of hypotension and subsequent fluid therapy with remimazolam anesthesia may mitigate the hemodilution associated with induction and ANH [4, 20]. However, our study was designed with only a remimazolam patient population. Further clinical studies are required to determine whether the harvest volume of ANH is higher in patients administered with remimazolam than in those treated with conventional anesthetics.

Consistent with previous studies [4, 21, 22], a reduction in RBC was observed in the ANH group in during both intraoperative and postoperative periods. Additionally, the incidence of postoperative bleeding was lower in this study. It is speculated that the preserved hemostatic function resulted in a reduction in postoperative bleeding in the ANH group. Recently, Henderson et al. evaluated the impact of ANH volume on allogeneic transfusion amounts using propensity score matching [4]. Their study showed that postoperative transfusion was significantly lower in the high-volume ANH group than in the control group (median blood volume: 1100 and 400 mL, respectively), although platelet counts at ICU admission between the two groups were not significantly different. Taken together, fresh platelets in ANH blood might contribute to postoperative hemostatic function while avoiding CPB-related platelet dysfunction [23, 24].

Our study had several limitations. First, this was a retrospective, observational study. Although the correlations between ANH and allogeneic transfusion were significant after adjusting for age and preoperative hematocrit levels, unobserved confounders and residual bias may have influenced our results. The ratio of deep hypothermic circulatory arrest in the control group was slightly higher than in the ANH group, although not significant. This may have emphasized the difference of transfusion product usage between the two groups. ANH is less likely to be performed for patients with preoperative anemia, but those patients may have other comorbidities. The patients with preoperative anemia might be in the high-risk bleeding group. Second, this study included only a limited number of patients. Because the availability of ANH may depend on the type of surgery, additional studies with larger patient populations are required. Finally, ANH implementation may trigger RBC transfusion by the patient care team. Perfusionists may transfuse RBC more restrictively during CPB in patients on ANH, thereby enhancing the reduction effect of allogeneic transfusion.

In patients with CPB, ANH can reduce the perioperative use of allogeneic transfusions and postoperative bleeding. Because of its minimal impact on hemodynamic parameters during blood collection, remimazolam is a useful anesthetic for patients with low BMI. Further clinical studies are warranted to verify whether remimazolam is preferable to conventional anesthetics for ANH in patients with cardiac diseases.

Author contributions YT: Recruit patients and collected and analyzed the data. RY: Revise and approve the final draft of the manuscript. TS: revise and approve the final draft of the manuscript. FA: Revise and approve the final draft of the manuscript. SO: Conception and design of the study and wrote the first draft of the manuscript.

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Data availability Data will be available upon reasonable request to corresponding author.

Declarations

Conflict of interest The authors declared no conflict of interest.

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