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Early red blood cell transfusion and the occurrence of intraventricular hemorrhage in very preterm infants

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ABSTRACT

Background: Preterm infants are at risk of developing both intraventricular hemorrhage (IVH) and anemia of prematurity. Several studies reported an association between early postnatal red blood cell (RBC) transfusion and IVH, however the timing and causality between these two remains unclear.
Aims: To describe the temporal sequence between administration of early RBC transfusion (within the first week of life) and diagnosis of IVH in very preterm infants.
Study design: Retrospective single center case-series.
Subjects: 132 very preterm infants (<32 weeks' gestation), admitted to a level III neonatal intensive care unit, studied with serial cranial ultrasound (CUS), and diagnosed with any grade of IVH.
Outcome measures: Number and timing of early RBC transfusions in relation to the timing of IVH.
Results: Median time of IVH diagnosis was 20.5 h after birth (interquartile range [IQR], 6.25–49.00 h). Of those who received an early RBC transfusion (36 %, 47/132), only 15 % (20/132) received it before the IVH diagnosis. Infants with RBC transfusion before IVH more frequently had lower birth weight, received less fequently antenatal steroids, required more often invasive mechanical ventilation and surfactant administration, had more often hypo- and hypercapnia, and received more fluid boluses, NaHCO3, and inotropes compared to the rest.
Conclusions: In the majority of infants, IVH was already present at the time of the first RBC transfusion. Studies including pre- and post RBC transfusion CUS are needed to assess the effect of early RBC transfusions on the development of IVH in preterm neonates.

1. Introduction

Germinal matrix hemorrhage and intraventricular hemorrhage, from now on referred to as IVH, is an important complication of prematurity and can lead to serious developmental problems in later life [1]. In preterm infants, IVH usually develops within the first 72 h after birth, and in the majority of cases even within 6–24 h after birth, making this a crucial time window for preventing this complication and its long term sequelae [1–3].

The pathogenesis of IVH involves many factors associated with the susceptibility of rapidly maturing germinal matrix vessels [1]. These vessels undergo significant remodeling within the first few days after birth and can be damaged by a variety of intra-, extra- and vascular factors. Intravascular factors include those that cause fluctuations in cerebral blood flow, increase in cerebral venous pressure and platelet and coagulation disturbance. Extravascular factors include deficient vascular support, fibrinolytic activity and postnatal decrease in extravascular tissue pressure and vascular factors including the vulnerability of matrix capillaries [4].

Some studies have found early red blood cell (RBC) transfusion to be a risk factor for IVH [5–7]. There seems to be an association, but the causal association between RBC transfusion and IVH remains a matter of debate as IVH itself can lead to anemia and the need for RBC transfusion [8].

Abbreviations: IVH, Intraventricular hemorrhage; RBC, Red blood cell; CUS, Cranial ultrasound; GA, Gestational age; pCO2, Partial pressure of carbon dioxide; PVHI, Periventricular hemorrhagic infarction; PHVD, Posthemorrhagic ventricular dilatation.

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To be able to differentiate whether IVH already developed before or shortly after a RBC transfusion, a serial cranial ultrasound (CUS) protocol including early postnatal scans is required. Serial CUS is an important bedside tool for the diagnosis of IVH [9]. However, in many studies describing an association between RBC transfusion and IVH, details on the timing and frequency of CUS scans were not provided or we can only assume that there was a relatively large time interval between CUS scans [6,7,10]. In these studies, infants who received transfusions had a lower gestational age (GA) and birth weight, and this also has an impact on the incidence of IVH. Nevertheless, some studies still reported a decrease in both the frequency of RBC transfusions as well as the frequency of IVH after the application of new, more restrictive transfusion guidelines [7,10].

The aim of this study was to investigate the relationship and time dependence between the need for early RBC transfusion (within the first week after birth) and the development of IVH in a population of very preterm infants who underwent early and serial CUS scans within the first postnatal week, according to a standard protocol. Second, we aimed to assess whether infants who received an early RBC transfusion, before IVH diagnosis, were more likely to have additional risk factors for the development of an IVH.

2. Materials and methods

2.1. Study design and population

This study was conducted as a retrospective case-series analysis from a consecutive cohort of very preterm infants (GA <32 weeks) who were admitted between May 2015 and May 2019 to the Leiden University Medical Center (LUMC), the Netherlands, a level III neonatal intensive care unit (NICU). All infants who were diagnosed with any grade of IVH within the first postnatal week were included in this study. Exclusion criteria were: IVH diagnosis after the first week or antenatal brain injury. Approval with a waiver of informed consent was granted by the institutional review board of the LUMC (G19.072).

2.2. Transfusion protocol

During the study period, the routine protocol for RBC transfusion during the first postnatal week described a hemoglobin threshold <7.5 mmol/l (Hb <12,1 g/dl) for a preterm infant on mechanical ventilation or receiving another form of respiratory support and below <6.5 mmol/l (Hb <10,5 g/dl) in any other preterm infant during the first week of life. The NICU guidelines advised administering a RBC transfusion volume of 15 ml/kg body weight over a period of 3 h for preterm infants with a GA ≥26 weeks and 6 h for those with a GA <26 weeks. All RBC transfusions were administered by a peripheral line.

2.3. Cranial ultrasound protocol

CUS examinations were performed by the attending neonatologist according to a standardized protocol for very preterm infants. The routine CUS protocol for preterm infants included an admission scan, performed within the first 24 h after birth and follow up scans on day 3 and day 7. Additional scans were performed when a patient was clinically unstable or if an IVH was suspected. Afterwards, CUS was performed weekly within the first month and then biweekly until discharge or term equivalent age. Images were obtained using the anterior fontanel and recorded in at least six coronal and five sagittal planes. In addition, images via the mastoid fontanel were obtained [9]. Before 2015, CUS was performed using an Aloka α ultrasound system (Hitachi Medical Systems Holding AG, Switzerland). From 2015 onwards, a Canon Aplio 400 or Aplio i700 system (Canon Medical Systems B.V., the Netherlands) was used. All CUS scans were performed by a trained neonatologist/physician assistant. All images were stored online and available for review and measurements (Clinical Assistant, RVC, The Netherlands). For this study, the scans of infants diagnosed with IVH were reviewed by two neonatologists with a longstanding experience in neuroimaging (LSdV and SJS) who were unaware of the clinical characteristics of the individual infants and the transfusion history.

2.4. Data collection and definitions

Data were extracted from hospital medical records, focusing on the period between birth and 48 h after IVH diagnosis. To determine group homogeneity, the following baseline neonatal characteristics were collected for all study participants: GA, birth weight, sex, delivery mode (i.e., caesarean section or vaginal delivery), and multiple gestation. The following factors defined in the literature as additional risk factors for the occurrence of IVH were recorded: lack of a (full) course of antenatal steroids, umbilical cord blood pH, Apgar score at 5 min, postnatal transport. For the following factors which may also occur later during admission, only the occurrence before the diagnosis of IVH was noted: hematocrit, hemoglobin level and platelet count (i.e. the first measurement taken and the lowest result obtained before the diagnosis of IVH), surfactant administration, need for invasive mechanical ventilation, inotropic support, fluid boluses or NaHCO3 suppletion and occurrence of pneumothorax, hypoglycemia (i.e. <30.6 mg/dl level measured during the first hour postpartum, <39.6 mg/dl level measured during 1–3 h postpartum, <46.8 mg/dl after 3 h postpartum), hypocapnia (i.e. pCO2 < 37,5 mmHg) or hypercapnia (i.e. pCO2 ≥ 60,0 mmHg) or sepsis confirmed by a positive blood culture [4,11–19].

Data pertaining to IVH included the time of diagnosis (based on the date and time of the CUS scan when an IVH was first detected and if applicable the date and time of the last normal CUS before diagnosis). IVH was further classified into grades I-III, according to Volpe, with a separate notation for periventricular hemorrhagic infarction (PVHI) and/or posthemorrhagic ventricular dilatation (PHVD) [20]. High-grade IVH (severe IVH) was defined as IVH grade III or any grade of IVH complicated by PVHI and/or PHVD.

We recorded the administration of RBC transfusions in the first week after birth, referred to as early transfusions. Data pertaining to the transfusion history included the number of RBC transfusions in the first postnatal week, whether RBC transfusions were administered according to the protocol, and the timing of RBC transfusion in relation to the timing of IVH diagnosis with a separate notation for transfusions given before or within 48 h after IVH diagnosis. We were able to evaluate the administration of RBC transfusions through the use of electronic files, in which as soon as a transfusion is started, a record of this is made along with the speed and duration of the RBC transfusion.

2.5. Statistical analysis

All data were analyzed with the SAS OnDemand for Academics using descriptive statistics (SAS Institute Inc., SAS Campus Drive, Cary, North Carolina, USA). Categorical data were presented as numbers and percentages, continuous variables as means with standard deviation (SD) for normally distributed data, and as medians with interquartile range (IQR) for non-normally distributed data.

3. Results

3.1. Demographic characteristics

Of the 139 very preterm infants admitted during the study period who were diagnosed with IVH, 132 infants were included in the study. Seven infants were excluded based on the following criteria: antenatal brain injury ($n = 1$), and time of diagnosis >7 days after birth ($n = 6$) (Fig. 1). Within the study population, 64 % (85/132) had low-grade IVH (30 %; 40/132 grade I and 34 %; 45/132 grade II) and 36 % (47/132) had high-grade IVH (14 %; 18/132 grade III, 22 %; 29/132 IVH complicated by PVHI and/or PHVD).

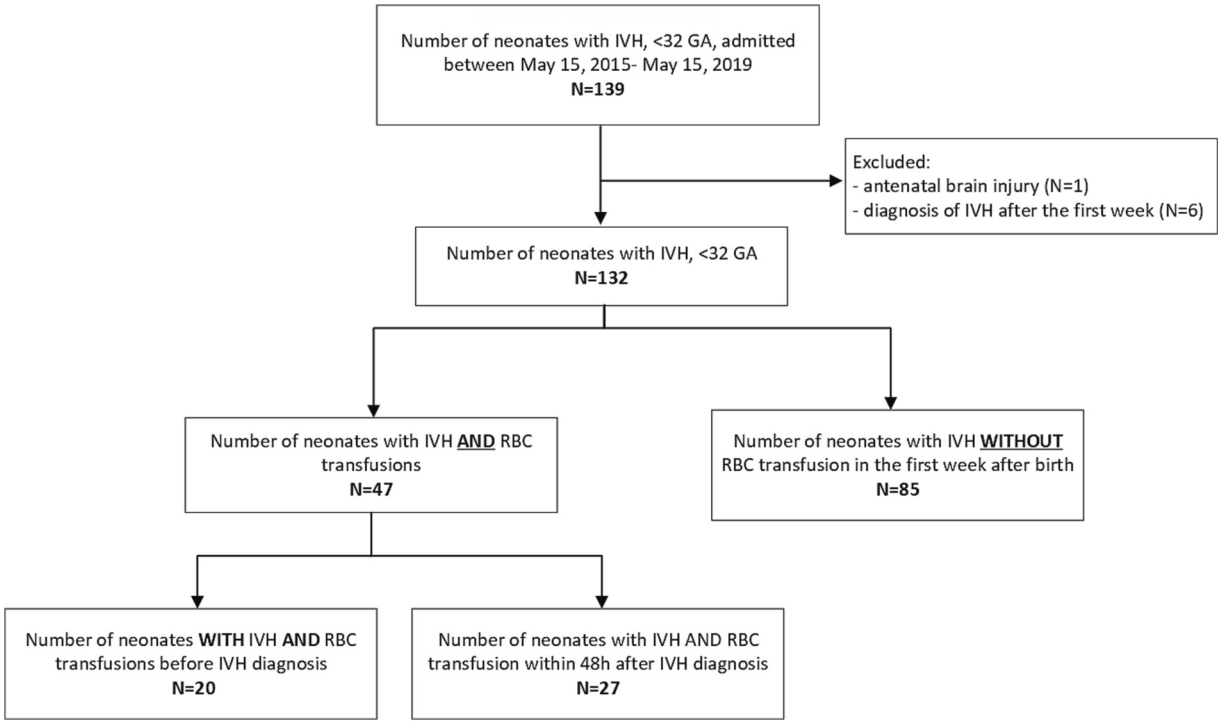

Fig. 1. Flowchart of the study population
Abbreviations: IVH, intraventricular hemorrhage; GA, gestational age; RBC transfusion, red blood cell transfusion.

The majority (64 %, 85/132) of infants with IVH did not receive a RBC transfusion. Of those who received an early RBC transfusion (36 %, 47/132), only 15 % (20/132) received a RBC transfusion before the IVH diagnosis, while 20 % (27/132) of infants received a RBC transfusion within 48 h after IVH diagnosis. We compared the baseline characteristics and risk factors for IVH between infants who received a RBC transfusion before IVH diagnosis with those who did need a RBC transfusion within 48 h after IVH diagnosis or did not need a RBC transfusion in the first postnatal week at all (Table 1). Infants who had a high grade IVH more often received RBC transfusion within 48 h after IVH.

3.2. Red blood cell (RBC) transfusions

Of the 132 infants with IVH, 47 (36 %) received an early RBC transfusion in the first postnatal week. Twenty of 47 infants (42.6 %) received the first RBC transfusion before the diagnosis of IVH and 27 (57.4 %) within 48 h after the diagnosis of IVH. (Table 2) Of the 71 transfusions, in all cases the indication was according to the protocol and 83 % were also administered according to the guidelines. In 17 % there was a slight deviation in speed and/or volume.

3.3. Time of IVH diagnosis

Of all IVH, 78 (59 %) were diagnosed during the first CUS examination. Median time of IVH diagnosis was 20,5 h (IQR 6,25-49,00). Thirty-three infants (25 %) were diagnosed with IVH within the first six hours, 71 (54 %) within the first 24 h, and 120 (91 %) infants by the end of the fourth postnatal day (Table 3). The average number of CUS scans performed between delivery and diagnosis of IVH was 2 scans.

3.4. Risk factors associated with RBC transfusion before IVH

The mean birth weight in infants who received a RBC transfusion before IVH diagnosis was lower compared to infants with RBC transfusion 48 h after IVH and the ones without RBC transfusion in the first week after birth. Antenatal steroids were less common and invasive mechanical ventilation was more common in infants with early RBC transfusion, before IVH diagnosis. The incidence of hypocapnia was also higher and lower platelets counts were more common in this group. Furthermore, these infants more often received fluid boluses, NaHCO3, and inotropes. (Table 1).

4. Discussion

This study aimed to describe the association and time dependence between the administration of early RBC transfusion and the occurrence of IVH in very preterm infants. Only 20/132 (15 %) of the infants received a transfusion before the CUS diagnosis of IVH. Therefore, in most infants RBC transfusion was only performed after IVH was already diagnosed. Using a dedicated CUS protocol, we were able to show that 54 % (71/132) of all IVH in our study population were diagnosed within 24 h after birth, and 91 % (120/132) within the first 4 days, with the median time of IVH diagnosis being 20,5 h (IQR 6.25–49.00 h). Our results are in line with previous literature where onset of IVH is described in at least 50 % of affected infants on the first day after delivery, and about 90 % of cases before 72 h [23].

.An association has been reported in the literature, among very preterm infants, between RBC transfusion in the first days after birth and the development of IVH. Some of these studies examining the effect of RBC transfusion on IVH suggest that transfusion may have a negative effect by triggering an inflammatory process or through hemodynamic disruption. Alternative possibilities could be related to mechanical factors as (adult) donor cells are less deformable than fetal red blood cells and therefore more likely to compromise brain perfusion and to changes in hydrostatic pressure as a transfusion is also a fluid bolus. In addition, deficiency of nitric oxide in stored adult red blood cells may predispose to vasoconstriction and ischemic insults [6,7,9,10,21]. Lastly, the fact that most infants who receive RBC transfusion will have a low hematocrit prior to transfusion may be a risk factor by itself, as it can be associated with a lower intravascular volume and cerebral hypoperfusion [21]. Some of the studies try to explain their results as a

Table 1
Patient characteristics.

Characteristics	Infants with RBC transfusion before IVH diagnosis ($n = 20$)[a]	Infants with RBC transfusion within 48 h after IVH diagnosis ($n = 27$)[a]	Infants without RBC transfusion in first week after birth ($n = 85$)[a]
Any intraventricular hemorrhage, No. (%)	5(25)	5 (19)	30 (35)
grade I	8 (40)	7 (26)	30 (35)
grade II	4 (20)	6 (22)	8 (9)
grade III	3 (15)	9 (33)	17 (20)
any grade of IVH complicated by PVHI and/or PHVD			
Gestational age at birth, median (IQR), wk	26 (4)	26 (4)	28 (3)
Birth weight, mean (SD), g	960 (333,6)	1101 (438)	1306,8 (400)
Sex, No. (%)			
Female	4 (20)	13 (48)	40 (47)
Male	16 (80)	14 (52)	45 (53)
Singleton, No. (%)	11 (55)	22 (81)	63 (74)
Vaginal delivery, No. (%)	11 (55)	13 (48)	29 (34)
inborn, No. (%)	18 (90)	24 (89)	79 (93)
Antenatal steroids, No. (%)	14 (74)	24 (89)	82 (98)
Apgar score at 5 min, median (IQR)	7 (2)	7 (2)	8 (3)
Surfactant administration, No. (%)	14 (70)	15 (56)	37 (44)
Invasive mechanical ventilation, No. (%)	17 (85)	16 (59)	27 (32)
Pneumothorax, No. (%)	0 (0)	0 (0)	2 (2)
Hypercapnia, No. (%) (pCO2 $\geq$ 60,0 mmHg)	14 (70)	12 (44)	44 (52)
Hypocapnia, No. (%) (pCO2 $<$ 37,5 mmHg)	17 (85)	15 (56)	35 (41)
arterial umbilical pH, median (IQR)	7,24 (0,14)	7,21 (0,12)	7,21 (0,12)
Hct level, median (IQR)			
First measurement	0.39 (0,08)	0.42 (0,08)	0.49 (0,11)
lowest measurement	0.27 (0,07)	0.37 (0,06)	0.43 (0,07)
Hgb level, median (IQR), g/dl			
First measurement	13,2 (1,7)	14,3 (1,9)	16,4 (2,2)
lowest measurement	9,7 (0,34)	12,6 (1,2)	14,7 (1,5)
platelet count, median (IQR)	123 (26)	113,5 (11)	117 (32)
$<150 *10^{-9}/l$	85 (19)	89 (17)	80,5 (29)
$<100 *10^{-9}/l$	40 (0)	-	24 (40)
$<50 *10^{-9}/l$			
Hypoglycemia, No. (%)	4 (20)	5 (19)	25 (29)
Fluid boluses administration, No. (%)	13 (65)	9 (33)	18 (21)
NaHCO3 administration, No. (%)	9 (45)	8 (30)	9 (11)
Inotrope use, No. (%)	5 (25)	3 (11)	5 (6)
Confirmed sepsis, No. (%)	0 (0)	0 (0)	4 (5)

Abbreviations: SD, standard deviation; IQR, interquartile range; No., number; %, percentage; IVH, intraventricular hemorrhage; PVHI, periventricular hemorrhagic infarction; PHVD, posthemorrhagic ventricular dilatation; wk., week after birth; g, grams; pCO2, partial pressure of carbon dioxide; mmHg, millimeters of mercury; Hct level, hematocrit level; Hgb level, hemoglobin level;

Table 2
Total number of red blood cell (RBC) transfusions administered during the first week after delivery.

First RBC transfusion	Number of patients	Total number of early transfusions		
		Before IVH diagnosis	Within 48 h after IVH diagnosis	$>$ 48 h after IVH diagnosis
Before IVH diagnosis, n	20	24	7	2
Within 48 h after IVH diagnosis, n	27	–	27	11
$>$ 48 h after IVH diagnosis, n	–	–	–	–

Patients categorized by timing of their first RBC transfusion.
RBC- red blood cell; IVH- intraventricular hemorrhage; n-number;

Table 3
Timing of IVH diagnosis represented in hours of life.

Days of life	Hours of life	Number of IVHs diagnosed	Percentage (%)	Cumulative percentage (%)
	0-6 h	33	25 %	25 %
1	6-12 h	19	14 %	39 %
	12-24 h	19	14 %	54 %
2	24-48 h	28	21 %	75 %
3	48-72 h	14	11 %	86 %
4	72– 96 h	7	5 %	91 %
5	96-120 h	7	5 %	96 %
6	120–144 h	5	4 %	100 %

decline in IVH rate after the implementation of a more restrictive transfusion protocol suggesting a causal relationship between the administration of RBC transfusion and the development of IVH. However, to confirm that this effect reflects true causality and not merely an association one has to be sure that the IVH only occurred after transfusion and was not already present at the time of transfusion. Moreover, as IVH itself can also lead to lower hematocrit values, the need for RBC transfusion may even be a consequence of IVH occurrence. For a better understanding of this complex series of events a dedicated CUS protocol with serial scanning shortly before and after transfusion is required. In many studies, details on the CUS protocol and timing of scans are lacking.

RBC transfusion thresholds and protocols of administration vary widely across NICUs. Therefore, it is difficult to compare studies describing the frequency of administering RBC transfusion [22]. There may have been some differences between the RBC transfusion strategy in our study and those from other studies that may have influenced the association between RBC transfusion and IVH. In our population, 36 % of infants received RBC transfusion in the first week of life, which is a lower percentage than reported previously [10–12]. Moreover, Christensen et al. (2014) reported that 59 % of infants diagnosed with IVH had transfusions within the first 24 h of life, while in our study this rate is much lower (14 %, 18/132) [10]. Therefore, it seems that we already used more restrictive transfusion guidelines and may have selected patients with lower hemoglobin levels and/or higher illness severity for early transfusion.

As the etiology of IVH is multifactorial and many early postnatal factors influence the risk of IVH, we compared the clinical risk factors between infants who had received a RBC transfusion before IVH diagnosis and those who did not. In infants who received the transfusion before IVH diagnosis, a full course of antenatal steroids was less often given to the mother. Also these infants, were significantly younger at

birth, had lower birth weight and nearly all (85 %) required mechanical ventilation. They also received inotropes, fluid boluses and bicarbonate more frequently. This suggests that overall the infants who were in need of early RBC transfusion and developed IVH were clinically unstable and had higher illness severity. Therefore, also in these cases, the true causal relationship between the administration of RBC transfusion and the development of IVH remains uncertain.

We recognize that our study has limitations. First, we used a retrospective design and therefore data collection was limited to information obtained as part of standard care. In addition, our study design (case series) is not suitable for hypothesis testing, so we decided to describe the differences between the patients groups using only descriptive statistics. Although we had access to more dedicated, serial CUS data compared to other studies, it still remains difficult to determine the exact time of IVH occurrence [6,7,9–11], .as IVH is usually asymptomatic. Therefore we could only narrow the time window to a moment between the last normal CUS scan and the next scan on the basis of which the IVH was diagnosed. It should be noted that despite our efforts, there were still several hours periods between scans in which IVH could occur. Moreover, the retrospective design of our study hampered the use of a structured and continuous scoring of illness severity before IVH and the lack of a control group of infants without IVH did not allow statistical analysis of the relation between illness severity, other IVH risk factors, early transfusion and occurrence of IVH.

For the future, a prospective study with standardized daily ultrasound scanning during the first 4 days and also scanning immediately before and within 24 and 48 h after RBC transfusion and taking into account the presence of other risk factors may be helpful to further explore the series of events taking place between birth, early transfusion and IVH.

5. Conclusion

Preterm infants are at risk of IVH, which is a serious complication that usually develops within the first hours-days after birth. The findings of our study, show that in the majority of patients IVH was already present at the time of transfusion, whereas the infants who received transfusion before the diagnosis of IVH were much younger at birth and often experienced other risk factors. Pre- and post RBC transfusion CUS is needed to assess the effect of early RBC transfusions on the development of IVH in preterm neonates.

CRediT authorship contribution statement

Aleksandra Skubisz: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Linda S. de Vries:** Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Sophie Jansen:** Data curation, Formal analysis, Project administration, Writing – review & editing. **Hilde van der Staaij:** Data curation, Formal analysis, Methodology, Validation, Writing – review & editing. **Enrico Lopriore:** Conceptualization, Methodology, Resources, Supervision, Writing – review & editing. **Sylke J. Steggerda:** Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

None.

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