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Cerebral blood flow alterations associated with high volume caudal block in infants

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Abstract

Background: High-volume (1.5 ml kg^{-1}) caudal block in infants results in major reductions of cerebral blood flow velocity (CBFV) and cerebral oxygenation, caused by rostral CSF movement which increases intracranial pressure. The primary aim of this study was to determine the relationship between injected volume and CBFV changes. We hypothesised that this volume–blood flow relationship would have a similar albeit inverted shape to the well-known intracranial pressure volume–pressure curve.

Methods: Fifteen subjects, age 0–6 months, mean (range) weight 4.9 (2.1–6.4) kg, were studied. A 1.5 ml kg^{-1} caudal injection of 0.2% ropivacaine was administered in three phases separated by two pauses. Subjects were randomised into five groups, in whom the pauses were implemented at different pre-set proportions of the total injected volume. Middle cerebral artery Doppler ultrasonography was used for CBFV measurements (V_{max}, peak CBF velocity; V_{min}, lowest CBF velocity; velocity time index). Mean flow velocity, pulsatility index, and resistivity index were calculated, and haemodynamic parameters were recorded.

Results: CBFV parameters decreased in all patients. The most affected parameter, V_{min}, was reduced by ~50% (range 15–68%) compared with baseline. There was a nonlinear relationship between the volume of the first phase injection and the CBFV measurement during the first pause. Across all time points, there was a linear relationship between volume administered and CBFV. Systemic haemodynamic parameters remained stable throughout the study.

Conclusions: Injection pauses appear to attenuate adverse CBFV increases during administration of a high-volume caudal block.

Keywords: children; infant; Doppler blood flow velocity, cerebral; intracranial pressure; local anaesthetic, ropivacaine; regional anaesthesia, caudal blockade

Editor's key points

- Caudal epidural injection of 1.5 ml kg^{-1} of local anaesthetic has been shown to cause a temporary reduction in cerebral blood flow and oxygenation.
- This is probably caused by a cranial shift of cerebrospinal fluid thereby raising the intracranial pressure and decreasing cerebral perfusion pressure.
- In the current study the same total volume was administered, but in three phases, with a pause between each phase, with blood flow velocity measurements after each phase.
- The pauses increased overall duration of the caudal injection, and attenuated the associated cerebral haemodynamic disturbances.

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We have shown that a bidirectional shift of cerebrospinal fluid ('the CSF rebound mechanism') plays an important role regarding the final spread of the injected local anaesthetic drug when performing a high-volume (1.5 ml kg^{-1}) caudal block.[1] Caudal injection causes a rostral shift of CSF from the spinal canal into the intracranial space, resulting in a transient increase of ICP,[2] which will temporarily reduce cerebral blood flow (CBF).[2] As the pressure in the spinal canal subsequently normalises, CSF returns to the spinal canal, forcing the caudally injected local anaesthetic in a cranial direction.[1] This rebound of CSF will reduce intracranial pressure (ICP) and allow partial normalisation of CBF.[2] The transient reduction of CBF is well tolerated by most children but could be potentially hazardous in children with already elevated ICP or intracranial pathology.

Many textbooks have graphically depicted the relationship between the volume of an intracerebral mass (e.g. haematoma or tumour) and ICP as a 'curvilinear' relationship. At low volumes, the relationship is linear, and ICP remains reasonably stable. As the volume increases the brain's compensatory mechanisms are exhausted, an inflection point is reached, and ICP increases exponentially as brain compliance reduces.

The primary aim of the present study was to determine the relationship between the injected caudal volume and the reduction of CBF, as assessed by changes in CBF velocity (CBFV) measured by ultrasound-guided Doppler measurements from the middle cerebral artery. Because the effect on cerebral perfusion in this setting is determined by similar principles to those used to explain the classic intracranial volume–pressure relationship,[3] we hypothesised that the injection volume–cerebral perfusion relationship would show a similar 'curvilinear' relationship with a potential inflection point beyond which the CBF reduction would become more apparent. Thus, the primary endpoint of the study was to define the threshold volume beyond which the injected volume will start to cause a more substantial reduction in cerebral perfusion. A secondary aim was to determine whether inclusion of two injection pauses would reduce the final effect on CBF as compared with data generated in our previous study (continuous non-stop injection).[2]

Methods

After approval from the Regional Ethics Committee: (No 2011/1928-31/3; Chairman Håkan Julius) and written parental informed consent had been obtained, 15 infants younger than 6 months and scheduled to undergo elective inguinal hernia repair were enrolled into the study. Exclusion criteria were lack of written consent and common contraindications for caudal block (e.g. malformations of the spine and coagulopathy).

Anaesthetic protocol

No premedication was used. Depending on whether a peripheral venous cannula was in place, anaesthesia was induced by intravenous injection of propofol (3 mg kg^{-1}) or inhalation of sevoflurane via a face mask (8% in oxygen). In those with no cannula, intravenous access was secured after induction of anaesthesia. Airway management was accomplished by insertion of a laryngeal mask or an endotracheal tube (muscle relaxation provided by rocuronium 0.6 mg kg^{-1}) and anaesthesia was maintained with sevoflurane 2.5% in air/oxygen for the duration of the study. CBFV has been found to be unaffected by sevoflurane at these concentrations in children.[4] HR and noninvasive blood pressure (NIBP) were measured throughout the study (Table 1).

Caudal block procedure

The child was placed in the left lateral decubitus position to allow caudal block placement. Care was taken to allow the spine to be in a neutral position, deliberately avoiding flexion of the spine. Approximately 5 min after induction of anaesthesia and when the end-tidal sevoflurane concentration had stabilised at 2.0–2.5%, the caudal block was performed using an aseptic technique.

The block was performed with a 25G caudal block needle (Epican; B. Braun, Melsungen, Germany). A total volume of 1.5 ml kg^{-1} of ropivacaine 0.2% was administered to all children using a 10 ml syringe. The injection was performed manually aiming for an injection speed of approximately 0.5 ml s^{-1} as in our previous studies.[1,2,5]

Randomisation

A sealed opaque envelope technique was used to randomly assign patients to one of five groups. In each group, the injection pauses were applied at pre-set proportions of the total caudal injection volume. The first pre-set pause occurred after injection of 20%, 30%, 40%, 50%, or 60% of the total volume of 1.5 ml kg^{-1}. Thereafter, a further 20% of the total dose was administered, followed by a second pause. The second pauses therefore occurred after injection of 40%, 50%, 60%, 70%, and 80% of the total injection volume of 1.5 ml kg^{-1}. The length of each pause was made long enough to allow high-quality ultrasound Doppler flow measurements.

Assessment of CBFV in the right middle cerebral artery

All ultrasound assessments were performed by one of the authors (PC) who was unaware of group allocation of the subjects. The same methodology was used as in our previous study.[2] Briefly, a duplex ultrasound Doppler system (Acuson SC 2000; Siemens, Mountain View, CA, USA) was used for the CBFV measurements. Through the temporal window, the right middle cerebral artery was identified using colour Doppler. The pulsed Doppler sample volume was placed in the vessel, and the probe position was adjusted to obtain an angle <20°, thus minimising the angle error to record the highest possible velocities. The probe was held manually in the same position during the study, and the position of the Doppler sample volume was checked before each recording. Four separate measurements were performed in each subject:

1. Baseline, before the start of the caudal injection
2. During predetermined pause 1 (i.e. after injection of 20%, 30%, 40%, 50%, or 60% of the total volume)
3. During predetermined pause 2 (i.e. after injection of another 20% of the total volume)

Table 1 Subject characteristics. Data are expressed as median (inter-quartile range).

Sex (M/F)	9/6
Postnatal age (weeks)	13 (10–19)
Gestational birth age (weeks)	33 (28–39)
Weight (kg)	4.9 (3.7–5.4)
Height (cm)	56 (52–60)

4. Immediately after the completion of the total injection (1.5 ml kg^{-1})

In each recording, three consecutive high-quality waveforms were selected for analysis. These three consecutive waveforms were subsequently analysed with the software Syngo Dynamics (Dragon Medical Practice, 2.12, Erlangen, Germany) measuring the average peak systolic (V_{max}) and end-diastolic (V_{min}) velocities and the velocity time integral (VTI). The mean values of the three waveforms were noted. The VTI represents the area under the ultrasound Doppler flow curve during one cardiac cycle.

The mean flow velocity (MFV) was calculated according to equation (1):

$$MFV = VTI \times HR/60 \quad (1)$$

Pulsatility index (PI) and resistivity index (RI) were calculated according to equations (2) and (3), respectively.

$$PI = (\text{peak systolic velocity} - \text{end-diastolic velocity})/\text{mean flow velocity} \quad (2)$$

$$RI = (\text{peak systolic velocity} - \text{end-diastolic velocity})/\text{peak systolic velocity} \quad (3)$$

After the completion of the transcranial flow velocity measurements, the study was concluded.

Primary aim

The primary aim of this study was to determine the relationship between the volume of caudal injection and the CBFV parameters assessed using ultrasound Doppler (expressed as decrease % from baseline). This should enable identification of the inflection point of the volume–CBFV curve, similar to an inverted classic volume–ICP curve.[3] The CBFV values obtained during the first predetermined injection pause (i.e. after injection of 0.3, 0.45, 0.6, 0.75, and 0.9 ml kg^{-1}) were used for this purpose.

Secondary aim

To determine whether the inclusion of two injection pauses would result in a reduced final effect on CBF velocities, as compared with our previously reported data, a second injection pause was performed (see above).

Statistical analysis

Based both on our previous experience and on theoretical considerations, we expected a nonlinear relationship between injected volume and CBFV parameters measured during the first predetermined injection pause. These data were thus subjected to a nonlinear curve fitting technique. Attempts at an exponential curve fit did not produce any relevant results, most likely because the data set contained too few data points. The data were therefore subsequently subjected to a commonly used general quadratic equation (polynomial relationship) to determine best curve fit:

$$Y = B_0 + B_1X + B_2X^2 \quad (4)$$

As it was impossible to predict the relationship for the entire data, including the two injection pauses, beforehand, we subjected these data both to linear regression and to nonlinear curve fitting alternatives.

Statistics and curve fittings were performed with GraphPad Prism 5.04 (GraphPad Software Inc., San Diego, CA, USA).

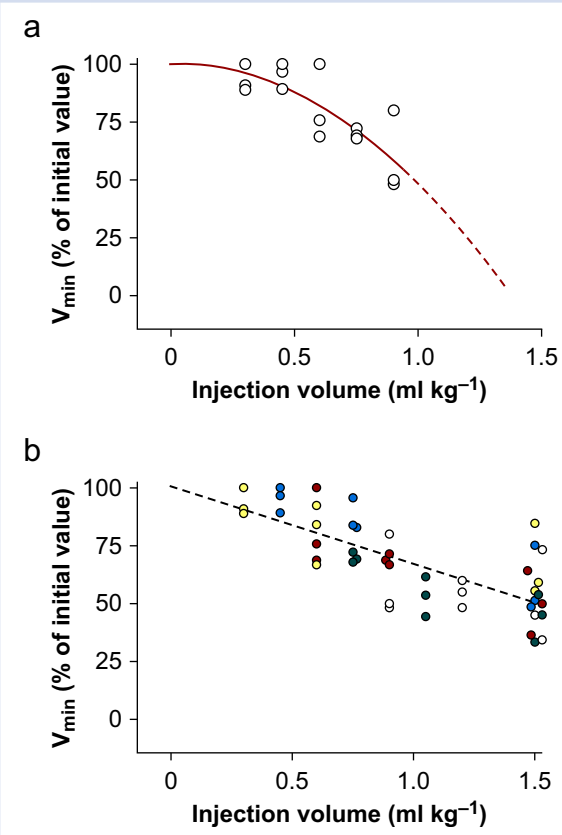

Fig 1. V_{min} (end-diastolic velocity) in relation to injected volume of local anaesthetic. (a) Initial uninterrupted injection. Solid line results from non-linear regression analysis; dotted line: extrapolation of the non-linear regression analysis. $R^2 = 0.747$. (b) For all measurement points. Study groups are differentiated by colour. Yellow: first stop at 20% and second stop at 40% of the injected volume. Blue: 30% and 50% of the injected volume. Red: 40% and 60% of the injected volume. Green: 50% and 70% of the injected volume. White: 60% and 80% of the injected volume. The dotted line is given by ordinary linear regression; $R^2 = 0.739$, $P \leq 0.0001$.

Ordinary (non-weighted) linear regression was used for evaluation of all data points. Spearman correlation test was used when comparing the time for injection with final blood-flow velocities and VTI. Wilcoxon matched-pairs signed rank test was used to test for differences in haemodynamic measurements.

Results

Subject characteristics are displayed in Table 1.

The median (inter-quartile range [IQR]) duration of predetermined pause 1 was 14 (11–18) s, and that of pause 2 was 14 (11–17) s. The median (IQR) duration of the full caudal injection was 41(34–48) s.

HR and NIBP remained stable during the study (Table 2).

Primary aim

The effects of the first phase of the caudal injections on V_{min} and MFV (normalised to pre-injection values) are shown in

Figures 2a and 3a. As can be seen in these figures, these relationships are 'curvilinear'. Injection volumes <0.5 ml were associated with modest or no changes in CBFV, whereas large injection volumes were generally associated with more profound CBFV effects. However, there are insufficient data for clear identification of an inflection point.

The individual equations for best curve fit for the various ultrasound Doppler flow derived parameters were:

$$V_{min}: Y = 96.2 + -0.01255X + -0.01255X^2 \quad (5)$$

$$VTI: \quad Y = 100.4 + -0.1690X + -0.009522X^2 \quad (6)$$

$$V_{max}: Y = 101.9 + -0.05575X + -0.007694X^2 \quad (7)$$

$$MFV: Y = 100.6 + -0.1633X + -0.00987X^2 \quad (8)$$

$$PI: \quad Y = 102.1 + 0.2335X + -0.01255X^2 \quad (9)$$

$$RI: \quad Y = 101.7 + 0.1169X + 0.001704X^2 \quad (10)$$

The associated R^2 values and 95% confidence intervals for each of the B_0, B_1, and B^2 values for these six equations are shown in Table 3.

As expected, V_{min} was the most affected parameter (Fig. 3a and Supplementary Figs 4a–6a).

Secondary aim

Figures 1b and 2b show the relationships among injection volume and V_{min} and MFV values, for all measurements and injection volumes. The best computer-based curve fit for the two-pause sequence was found to be linear. In this situation, V_{min} was associated with the largest slope, whereas V_{max} was minimally affected (see Figs 1b and 2b and Supplementary Figs 4b–7b).

The relationship between total injection time and V_{min} and MFV after the end of the injection is shown in Figure 3.

Results concerning V_{max}, VTI, PI, and RI are shown in the Supplementary material.

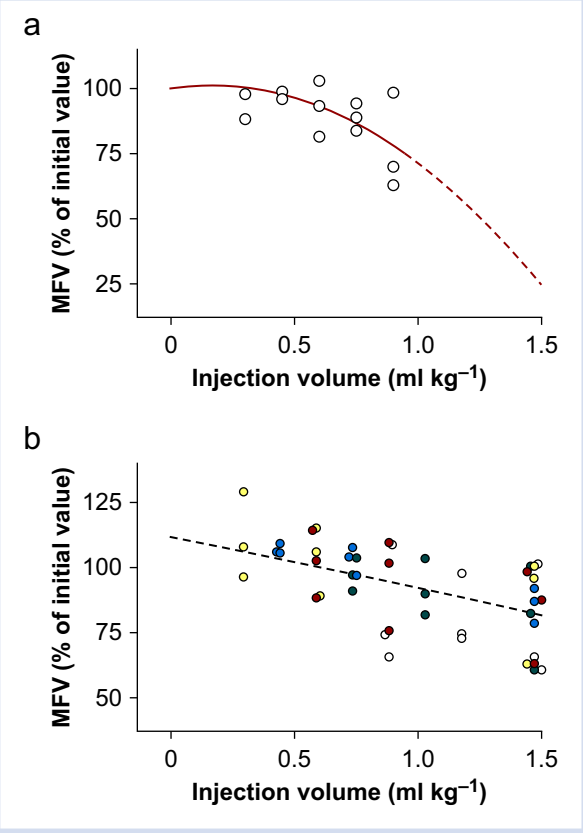

Fig 2. Mean flow velocity (MFV) in relation to injected volume of local anaesthetic. (a) Initial uninterrupted injection. Solid line results from non-linear regression analysis; dotted line: extrapolation of the non-linear regression analysis. $R^2 = 0.467$. (b) For all measurement points. Study groups differentiated by colour. Yellow: first stop at 20% and second stop at 40% of the injected volume. Blue: 30% and 50% of the injected volume. Red: 40% and 60% of the injected volume. Green: 50% and 70% of the injected volume. White: 60% and 80% of the injected volume. The dotted line is given by ordinary linear regression, $R^2 = 0.485$, $P = < 0.0001$.

Discussion

The main finding of the present study was that prolongation of the duration of caudal injection by the insertion of injection pauses during a high-volume caudal block results in an overall linear reduction of CBFV parameters. Injection pauses are also associated with smaller effects on CBFV parameters than those we previously found with uninterrupted caudal injection of the same total volume.

Table 2 Haemodynamics data. Data are expressed as median (inter-quartile range).

	Baseline	Full injection	P-value
HR (beat min^{-1})	152 (141–161)	152 (140–159)	0.09
$NIBP_s$	61 (52–76)	61 (59–69)	0.57
$NIBP_d$	33 (27–36)	31 (28–34)	0.08

NIBPs, Non invasive blood pressure systolic; NIBPd, Non invasive blood pressure diastolic.

Caudal blockade for paediatric surgery was first reported in 1933[6] and has since become the most frequently used paediatric regional anaesthesia technique worldwide.[4] Despite the existence of a large scientific body of literature on the topic, fundamental mechanistic and safety issues such as factors responsible for intraspinal spread and effects on cerebral hemodynamic, have not yet been fully elucidated.

We have shown that the injection of local anaesthetics will cause a substantial rostral shift of CSF. After an equilibrium phase the intraspinal pressure will return to pre-injection levels, which allows CSF to return to the caudal parts of the dural sac and thereby produce a second bulk flow of local anaesthetics in a cranial direction (i.e. 'the CSF rebound mechanism').[1]

The initial rostral transfer of CSF causes displacement of CSF into the intracranial space. Initially the increased volume will be compensated for by compression of intracranial venous structures and by shifts of the cerebral tissues made possible by the open status of the fontanelles. However, once

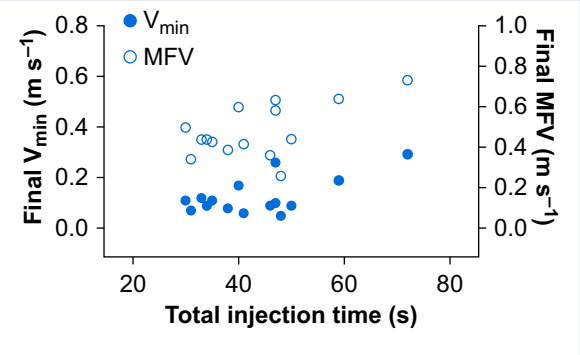

Fig 3. Effect of total injection time on final V_{min} (End-diastolic velocity) and final MFV (Mean flow velocity).

these compensatory mechanisms are exhausted, there might be a substantial increase in ICP that will negatively affect CBF and brain oxygenation (as assessed by near-infrared spectroscopy).[2] An increase in ICP after high-volume caudal block has also been verified using ultrasound assessment of the diameter of the optic nerve dural nerve sheath.[7]

Primary aim

Our results support our hypothesis of a nonlinear relationship between the volume of the first phase of the injection and the resulting effects on CBF. Our data do not support definition of a clear inflection point in this relationship. Volumes of up to 0.5 ml kg^{-1} appear to be associated with only limited effects on CBFV parameters (Figs 1a and 2a), but we do not have statistical confirmation of this, owing to the small sample size.

The inclusion of two injection pauses was associated with an overall linear relationship between total injected volume and resulting CBFV measurements (Figs 1b and 2b).

Secondary aim

In a previous study, during which a volume of 1.5 ml kg^{-1} was administered without any pauses, we found a final reduction of V_{min} of 89% compared with baseline values.[2] In the present study, we incorporated two pauses during the injection for the Doppler measurements. This two-pause technique was associated with only 50% reductions of V_{min} compared with baseline. It seems reasonable to assume that these injection pauses allow some modification of the physiological response seen in our previous study.

It is interesting that although we found a non-linear relationship between the volume of the first phase of the injection and CBFV parameters, there was an overall linear relationship between injection volume and CBFV across the different phases of caudal injection. Presumably, the duration of pauses was long enough to allow shifts of local anaesthetic drug, and/or CSF sufficient to attenuate the further declines in compliance during the second and third phases of injection.

Overall, we believe that the present study provides evidence in support of a slow and fractionated injection when performing a caudal block, not only to potentially decrease the risk of local anaesthetic systemic toxicity associated with unintentional intravascular injection[8,9] but also to reduce the adverse effects on the cerebral circulation. The transient reduction of CBF is well tolerated by most children but could be potentially hazardous in children with already elevated ICP or intracranial pathology.

Study design issues

First, in line with normal clinical practice, anaesthesia was induced either by inhalation of sevoflurane or intravenous injection of propofol. Theoretically, this could potentially influence ICP. However, as only one injection of propofol was given, we believe that any influence of the propofol injection performed 5–10 min before the initial baseline measurements is negligible.

Second, despite the limited number of data points, a non-linear fit between primary injected volume and the effects on CBFV parameters was observed. A larger number of data points would obviously have been for the better and might have been able to establish an exponential relationship, but we believe that our results support the hypothesised non-linear relationship between the volume of the first phase of the caudal injection and the resulting effects on CBFV parameters.

Third, as in our previous studies we have investigated CBFV parameters and not ICP *per se* in this context. However, we believe that we already have shown that the changes in CBFV parameters are secondary to increases in ICP caused by the caudal injection.[1,2] That caudal injections are associated with increases in ICP has also been clearly shown by Lee and colleagues.[7] From a physiologic and clinical point of view, CBF is a more important factor for cerebral function than ICP *per se*; thus, we believe that assessing alterations in CBF is more important than assessing absolute changes in ICP.

Table 3 Relevant parameters related to the best curve fit when applying the generic quadratic equation: $Y=B_0+B_1X+B_2X^2$. R^2 and 95% confidence interval (CI) are presented. For parameter abbreviations, please see the Methods section. PI, pulsatility index; RI, resistivity index; VTI, velocity time integral.

Parameter	R^2	B_0	95% CI	B_1	95% CI	B_2	95% CI
V_{min}	0.7473	96.2	90.78 to 101.6	−0.4355	−0.6162 to −0.2608	−0.01255	−0.02116 to −0.003931
VTI	0.4396	100.4	95.04 to 105.7	−0.1690	−0.3415 to 0.001584	−0.009522	−0.01818 to −0.0008625
V_{max}	0.2391	101.9	97.32 to 106.5	−0.05575	−0.1894 to 0.07794	−0.007694	−0.01513 to −0.0002594
MFV	0.4669	100.6	99.55 to 105.7	0.07979	−0.3270 to 0.00043	0.004028	−0.01814 to −0.001611
PI	0.6834	102.1	98.66 to 105.6	0.2335	0.1239 to 0.3432	0.005796	−0.0001708 to 0.003579
RI	0.7548	101.7	100.4 to 102.9	0.1169	0.07788 to 0.1560	0.001704	−0.00000687 to 0.01166

Fourth, the quadratic equation, and the number of patients and measurements, did not allow for a mathematical determination of a potential inflection point in the relationship between injected volume and CBFV parameters.

Finally, because systemic haemodynamic measurements were stable during the study period, any substantial change in cardiac output is in our opinion unlikely.[2] Furthermore, any major relaxation of the middle cerebral artery in response to a caudal block, in the setting of increased ICP and during a volatile anaesthetic, is unlikely. Although CBFV cannot immediately be translated into changes in actual blood flow we believe that the changes in CBFV seen in our study represent proportional changes in CBF.

In conclusion, CBF velocities increasingly decline after caudal injection of volumes of more than 0.5 ml kg^{-1}. Incorporation of injection pauses is recommended when performing a high-volume caudal block as this appears to lessen the effects on CBF.

Authors' contributions

Inclusion of patients: PC, JF
Data acquisition: PC, JF
Data analyses (including statistics): PC, ML
Writing of the manuscript: PC, ML, SE, PAL
Study supervision: ML, PAL
Study design: SE, PAL
Statistical analyses: SE
Study concept; PAL

Declarations of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.08.055.

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