Changes in fetal acid base status during intravascular transfusion

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SUMMARY Umbilical venous pH, PCO₂, PO₂, and base excess were measured immediately before and after 72 intravascular transfusions in 34 fetuses with erythroblastosis fetalis. In 67 uncomplicated transfusions, infused adult blood led to a mean (95% confidence intervals) fall in pH (0.037, CI 0.029 to 0.044) and base excess (2.03, CI 1.61 to 2.45) and a mean rise in PCO₂ (0.24 kPa, CI 0.13 to 0.35). These changes correlated significantly with the increase in fetal haemoglobin and packed cell volume. Five transfusions were associated with complications within six hours: intrauterine death in two, fetal distress necessitating delivery in two, and preterm labour in one. Two had pre-existing acidosis, whereas two of the three with normal blood gas and acid base measurements before transfusion had acute changes that were outside the normal ranges that had been established in uncomplicated transfusions.

During recent years direct access to the fetal circulation has not only established a role for the intravascular transfusion of anaemic fetuses with erythroblastosis fetalis,¹⁻³ but has also permitted closer study of the fetal environment in rhesus isoimmunisation.⁴⁻⁶ Antenatal intravascular transfusion, whether performed fetoscopically,^{1,7} or by needling under ultrasonographic control,^{3,8-11} carries risk to the fetus. The total risk of the procedure is the risk of fetal blood sampling¹² plus the risk of transfusion. Several reasons for fetal death after transfusion have been proposed, including changes in fetal oxygenation, and the direct cardiotoxic effects of the anticoagulant in donor blood.⁷

Normal ranges for fetal blood gas and acid base measurements have been described¹³ and used as a basis for intervention in compromised pregnancies.^{14,15} This study describes the normal ranges for changes in fetal blood gas and acid base measurements during uncomplicated transfusions, and assesses their use in predicting complications associated with transfusions.

Methods

Seventy two intravascular transfusions were performed for severe rhesus isoimmunisation by

needling of the umbilical vein under ultrasonographic control either in the intrahepatic portion or at the placental cord insertion. Thirty four fetuses, including one set of dichorionic twins, underwent one to four procedures at intervals of two to five weeks at gestational ages of 19 to 33 weeks. The technique, volume, and rate of transfusion have been described elsewhere.³ Before transfusion, the packed cell volume and haemoglobin concentration of each fetus were determined by a Coulter S Plus counter (Coulter Electronics Ltd, Luton, England), and an additional 250-300 µl of fetal blood was aspirated into a heparinised syringe for blood gas analysis. An intravenous rather than intra-arterial position of the needle was confirmed by the direction of flow of transfused blood seen on ultrasound scan. Donor blood was adult group O, Rh negative, and seronegative for cytomegalovirus. It had been collected within the previous 24 hours, cross-matched against maternal blood, and made up to a packed cell volume of 0.65 to 0.79. After the infusion the needle was flushed with 1 ml of normal saline and 1 ml of blood was aspirated and discarded. Samples for repeat haematological investigations, and a heparinised specimen for blood gas analysis were then taken. As in similar investigative studies, the additional volume of blood required was not considered to increase the risk to the fetus.⁶

especially as transfusion was replacing the aspirated volumes.

Blood gas analysis was performed within 20 minutes with an ABL 330 (Radiometer, Copenhagen, Denmark). Base excess was calculated from pH and PCO₂ using the Thews and Harnon-court nomogram to correct for haemoglobin concentration. Blood gas analysis was also performed on heparinised samples from nine donor packs immediately before use.

All haemoglobin concentrations before transfusion were ≥ 40 g/l, below which pronounced acidosis occurs.^{5,6} Sixty seven transfusions in 32 fetuses were uncomplicated and the pregnancies allowed to continue. Five procedures in five singleton fetuses, however, were complicated by delivery or death of the fetus within six hours of transfusion. One of these had ascites, as did 11 of the 67 uncomplicated procedures.

Fetoplacental volume was calculated using the formula $y=22.34+0.44x^2$ where x is gestational age.¹⁶ Changes in variables after transfusion are expressed as the post-transfusion value minus the pre-transfusion value. The normal distribution of changes in blood gas measurements was confirmed with histograms. Changes within transfusions were analysed statistically by the two tailed paired Student's t test, whereas comparisons between transfusions were considered as independent samples. Normal 95% data intervals were calculated from the formula: mean plus or minus $1.96 \times$ the standard deviation. Associations with haematological and obstetric data were assessed by Pearson's correlation coefficient.

Results

In 67 uncomplicated intravascular transfusions the mean pH and base excess fell, there was a rise in mean PCO₂, but the PO₂ did not change significantly (table 1). Significant, albeit weak, negative correlations were found between the changes in haematocrit and changes in pH ($r=-0.39$ $p<0.01$) and the change in base excess ($r=-0.34$, $p<0.01$),

and similarly between the changes in haemoglobin concentrations and changes in pH ($r=-0.34$, $p<0.01$) and changes in base excess ($r=-0.336$, $p<0.01$). Changes in both packed cell volumes and haemoglobin concentrations correlated positively with changes in PCO₂ ($r=0.323$, $p<0.01$, and $r=0.345$, $p<0.05$, respectively). There was no significant correlation of the acid base or blood gas changes with gestational age or volume transfused, except a weak positive correlation between the change in PCO₂ and transfused volume expressed as a percentage of fetoplacental volume ($r=0.260$, $p<0.05$).

To determine any effect of adult haemoglobin on blood gases, the changes in values in the initial transfusions (when the haemoglobin before transfusion is entirely fetal) were compared with subsequent transfusions when fetal blood may contain predominantly adult type haemoglobin (table 1). The drop in pH was slightly greater ($p=0.045$) during the initial transfusions, but changes in PCO₂, PO₂, and base excess were similar. In addition, there was no significant difference in changes in pH, PCO₂, PO₂, or base excess between transfusions in fetuses with pre-existing ascites and transfusions in those without ascites.

Donor blood had a mean (range) pH of 6.76 (6.57–6.94), PCO₂ of 16.82 kPa (15.7–17.9), and PO₂ of 3.96 kPa (3.25–4.67).

Five transfusions were associated with complications within six hours (table 2). There were two intrauterine deaths caused by the procedure. Fetal asystole occurred immediately after the procedure in case 1, responded at first to intracardiac and intramuscular adrenaline (0.5 ml of 1/100 000 at each site), but recurred within 15 minutes. Fetal pH at the time of fetal cardiac injection was 6.55. Transfusions in two patients (Cases 3 and 4) were complicated by fetal distress necessitating delivery. Fetal bradycardia occurred during the procedure in case 3 and was followed by a baseline tachycardia with late decelerations. Cord pH at caesarean section was 7.19. Case 4 developed variable decelerations in the presence of normal Doppler

Table 1 Mean (95% CI) changes in blood gas and acid/base measurements in uncomplicated transfusions for, all first, and subsequent procedures

	All procedures (n=67)	First procedures (n=27)	Subsequent procedures (n=40)
pH	-0.037* (-0.029 to -0.044)	-0.047† (-0.031 to -0.061)	-0.030† (-0.021 to -0.038)
PCO ₂	0.24* (0.13 to 0.35)	0.33 (0.10 to 0.55)	0.18 (0.07 to +0.29)
PO ₂	0.06 (+0.23 to -0.01)	0.29 (-0.07 to +0.65)	-0.10 (+0.06 to -0.27)
Base excess	-2.03* (-1.61 to -2.45)	-2.53 (-1.71 to -3.36)	-1.69 (-1.26 to -2.12)

*= $p<0.001$; †= $p<0.05$ (first compared with subsequent procedures).

Table 2 Five procedures in which complications occurred within six hours

Case No	Gestation (weeks)	Procedure No	pH before transfusion	Complications during procedure	Complications after procedure
1	26	2	7.42	Bradycardia	Intrauterine death within 15 minutes
2	32	2	7.38	None	Intrauterine death within three hours
3	32	5	7.37	Transient bradycardia	Fetal distress; emergency caesarean section at four hours
4	34	2	7.24	None	Variable decelerations; emergency caesarean section at six hours
5	30	3	7.20	None	Ruptured membranes; spontaneous delivery within four and a half hours

waveforms on testing of the umbilical artery. At 34 weeks, with borderline pre and post-transfusion pH, and with an increase in fetal ascites after the first transfusion, the decelerations were considered adequate grounds for delivery. Case 5 had persistent hydramnios and hydrops for six weeks. Although she did not complain of contractions, her membranes ruptured and she was fully dilated within three hours of the procedure. She was considered in

retrospect to have been in labour at the time of transfusion, this being the probable cause of the low fetal pH measurements (7.20 before, and 7.17 after the transfusion).

The figure shows a comparison of the changes in blood gas and acid base measurements in five complicated transfusions, with normal ranges established in uncomplicated transfusions. Two of the three procedures with a normal pH before transfusion, were associated with abnormal changes for pH, PCO₂, and base excess. No result for base excess was available in case 1 because of a fault in the machine.

Discussion

Transfusion of packed cells in human fetuses produced an acute fall in pH and base excess, and a rise in PCO₂. This drop in pH and base excess was the result of infusion of exogenous acids in donor blood rather than vascular spasm leading to hypoxaemia because there was no concomitant decrease in PO₂.

Given the degree of acidosis in donor blood (mean pH 6.76), the changes were minor due to the buffering of acidotic donor blood during fetoplacental circulation. A suggested advantage of transfusion into the umbilical artery instead of the umbilical vein as used in this study, is that before reaching the fetus the acidotic blood is buffered and oxygenated during passage through the placental circulation.^{2,3} Lactic acid was found earlier in samples from the umbilical artery than from the umbilical vein in patients with severe rhesus disease, consistent with a substantial placental capacity for buffering.⁵ In this study donor blood injected into the umbilical vein must have undergone one, and presumably several, fetoplacental circulations to affect acid base measurements in fetal blood collected at the same site. To determine the relative

Figure Changes in pH, PCO₂, PO₂, and base excess in complicated transfusions expressed against normal ranges for uncomplicated transfusions. Patient 1=◇, 2=○, 3=△, 4=●, 5=■. In patients 4 and 5 fetal acidosis was present before transfusion started.

buffering capacities of fetus and placenta, simultaneous samples from both umbilical artery and vein would be required after transfusion into either vessel. Such a study would pose ethical and technical difficulties.

Given the extremely high PCO_2 concentrations in donor blood, the rise in PCO_2 during transfusion is only small, again due to the buffering capacity of the placenta. The increase in PCO_2 and the fall in base excess together determine a tendency towards mixed respiratory and metabolic acidosis.

The lack of significant change in PO_2 reflects similar PO_2 s in donor and fetal blood. An increase in PO_2 might be expected in the presence of pre-existing hypoxia. There is, however, considerable evidence that the anaemic fetus maintains adequate tissue oxygenation until the haemoglobin concentration falls below 40 g/l^{4-6} and in this study no haemoglobin concentration was below 40 g/l . Chronic rises in umbilical vein PO_2 after transfusion have been reported in human¹⁷ and animal fetuses,^{18, 19} but may represent a compensatory rise in uteroplacental flow secondary to tissue hypoxia.¹⁷

The change in pH in first transfusions was slightly greater than in subsequent transfusions (-0.047 and -0.030 , $p=0.045$), but the difference in base excess was not significant. These findings are consistent with haemoglobin type having only a comparatively minor effect on blood gas and acid base measurements despite the greater affinity with oxygen of fetal compared with adult haemoglobin.¹⁷

Pre-existing fetal acidosis in two transfusions associated with complications suggested that the condition before transfusion rather than the intrauterine transfusion was responsible for delivery within six hours. In the remaining three complicated transfusions, two (cases 1 and 3) were associated with abnormally large changes in pH, PCO_2 , and base excess suggesting an adverse reaction beginning during the procedure. The change in PO_2 , however, was within normal limits, pointing to compromise of fetoplacental perfusion rather than of placental exchange. Although both fetuses developed bradycardia during infusion this was non-specific, occurring also in several uncomplicated transfusions. Intrauterine death three hours after transfusion in the remaining patient (case 2) was unexpected and unassociated with intraoperative complications or blood gas and acid base abnormalities. Necropsy was not performed. Although intraperitoneal transfusion may cause a fetal vagal bradycardia after the procedure, none of the five in which complications developed underwent the combined procedure of intravascular transfusion followed by intraperitoneal transfusion which has become our practice in order to prolong

intervals between transfusions (Nicolini *et al.*, unpublished observations).

Acute or subacute fetal distress or death, or both, after fetal blood sampling may be due to haematoma of the cord producing tamponade, fetomaternal haemorrhage, or exsanguination into the amniotic cavity. Additional mechanisms for acute or subacute complications after transfusion are poorly understood. Mackenzie *et al.* reviewed the possibilities and considered it unlikely that the cardiotoxic effects of citrate anticoagulant, potassium, and adenosine release from donor blood were responsible.⁷ The degree of acidosis in donor blood does not seem to be important. They used blood buffered to a pH of 7.20–7.35 and noted bradycardia during transfusion in six of 10 fetuses, eight of whom did not survive the perinatal period. This is in contrast to the paucity of complications in our series in which we used unbuffered blood.

This description of acute changes in acid base and blood gas parameters after transfusion in human fetuses permits calculation of normal ranges to predict complications directly related to the procedure. Closer postoperative monitoring of those with abnormal values who are likely to produce a live fetus may prevent fetal death by allowing timely intervention such as occurred in Case 3. We recommend the routine measurement of pH, PCO_2 , and base excess before and after intravascular transfusion.

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