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Fetal Pain

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Chapter 3

Fetal brain hemodynamic changes in intrauterine transfusion: influence of needle puncture site

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Abstract

Objectives Previous research has suggested that hemodynamic changes after in utero transfusion may be related to fetal stress. We tested the hypothesis that these hemodynamic changes are more pronounced when the needle is inserted in the fetal abdomen as compared to the umbilical cord root.

Methods Most intrauterine transfusions are performed by inserting a needle either in the umbilical cord root at the placental surface (PCI), or in the intrahepatic portion of the umbilical vein (IHV). We analysed prospectively collected data of all intrauterine blood transfusions (IUT) for fetal alloimmune anaemia (from 2000 to 2003), for which complete data were available on needling site and middle cerebral artery (MCA) Doppler flow velocity measurements before and immediately after the procedure.

Results Data of 57 IUTs were included. In 32 patients, the transfusion was performed through the PCI and in 25 patients through the IHV. Median Pulsatility index (PI) in the PCI group was 2.0 before and 1.7 after IUT ($p=0.011$), and in the IHV group 1.9 before and 1.5 after IUT ($p=0.001$). In both groups, MCA PI decreased significantly but there was no difference in decrease between the two groups ($p=0.99$).

Conclusions In anaemic fetuses undergoing transfusion, the observed fetal brain hemodynamic changes were independent of the site of needle insertion. The decrease in fetal MCA PI is therefore likely to be caused by the volume-expansion.

Introduction

Recent studies have suggested that the fetus is capable of exhibiting a stress response to intrauterine needling(1;2). Intrauterine transfusions are most commonly performed by inserting a needle either in the umbilical cord root at the placental surface, or in the intrahepatic portion of the umbilical vein of the fetus. Recently, intrauterine needling in the intrahepatic vein has been shown to result in alterations in blood flow profiles, which has been interpreted as a reaction to pain (3). Aim of our study was to confirm this hypothesis that fetal brain hemodynamic changes during intrauterine transfusion are more pronounced when the needle is inserted in the fetal abdomen.

Methods

The LUMC is the national referral centre for the treatment of fetal anaemia. Our methods for the treatment of severe alloimmune fetal anaemia have been described previously (4).

We searched our database for all intrauterine blood transfusions for fetal alloimmune anaemia, performed in the period from April 2000 to November 2003, in which before and immediately after the procedure, Doppler flow velocity waveforms from the middle cerebral artery were obtained. All measurements were performed by an experienced sonographer (E.S.), with an Acuson Sequoia (Mountain View, California, US) ultrasound machine with a 6MHz probe. All measurements were achieved in periods of fetal rest and apnoea. An angle $<20^\circ$ between the vessel and Doppler beam was used, and angle correction was applied. Doppler waveforms were obtained from three consecutive waveforms with similar appearance and a narrow band of frequencies and one of these was analysed. Women with singleton pregnancies undergoing clinically indicated (serial) intrauterine transfusions for fetal red cell alloimmunisation between 17 and 36 weeks were included. Cases with fetal hydrops were excluded. All women received pethidin 75 mg / promethazine 25 mg im and indomethacin 50 mg pr half an hour before the procedure. The site of the ultrasound-guided fetal blood transfusion (either the placental cord insertion, PCI, or the intrahepatic portion of the umbilical vein, IHV) was chosen by the operator on the basis of technical factors. All fetuses received the muscle-relaxant atracurium (0.4 mg/kg) intravenously immediately after taking the first fetal blood sample. Fetoplacental blood volume was calculated according to the method described by

Hoogeveen et al (5). Data were analysed using SPSS 14.0. Statistical analysis was performed using the paired and unpaired t-test and linear regression as appropriate. A P-value of <0.05 was considered statistically significant.

Results

Data of 57 intrauterine transfusions (IUTs) performed in 29 different patients were included. In 32 patients, the transfusion was performed in the PCI, and in 25 patients in the IHV. There were no fetuses with aneuploidy or structural anomalies on ultrasound examination. The characteristics of the study population are given in table 1. There were no significant differences between the groups except for a slightly longer duration of the procedure in the IHV group.

Table 1: Characteristics of the study population.

	PCI (N=32)	IHV (N=25)	P-value
Gestational age at IUT (weeks)	29 (17-35)	31 (23-36)	0.12
Hemoglobin before IUT (g/dl)	7.4 (3.9-11.6)	8.4 (3.9-13.8)	0.26
Hemoglobin after IUT (g/dl)	14.5 (12.6-17.1)	14.8 (12.9-17.6)	0.85
Transfusion volume (ml)	68 (14-125)	66 (20-131)	0.95
Transfusion volume (% Fetoplacental blood volume)	52 (33-76)	45 (14-72)	0.19
Duration of IUT (min)	24 (10-50)	28 (10-75)	0.047
EFW at IUT (grams)	1629 (204-3198)	1637 (700-2622)	0.10

Data are given as mean and range. PCI: placental cord insertion, IHV: intrahepatic vein, IUT: intrauterine transfusion, EFW: estimated fetal weight.

Mean Pulsatility Index for the middle cerebral artery (MCA PI) in the PCI group was 2.0 (range 1.2-3.9) before and 1.7 (range 1.0-2.4) after IUT. This decrease was statistically significant ($p = 0.004$). MCA PI in the IHV group was 1.9 (range 1.0-2.7) before and 1.5 (range 0.9-2.2) after IUT. This decrease was also statistically significant ($p = 0.001$). However, there was no difference in MCA PI decrease between the PCI and the IHV groups ($p = 0.99$). Delta PI in both the PCI and IHV group was not correlated to the delta change in relative fetal blood volume ($R^2=0.006$, $p=0.68$ and $R^2=0.10$, $p=0.12$)

Table 2 shows the MCA PI for both groups before and after IUT.

Table 2: MCA PI in both IHV and PCI group before and after intrauterine transfusion

	Mean MCA PI before IUT (SD)	Mean MCA PI after IUT (SD)	Mean difference (95% CI)	P-value
PCI (N=32)	2.0 (0.58)	1.67 (0.32)	0.34 (0.08-0.59)	0.004
IHV (N=25)	1.91 (0.45)	1.54 (0.32)	0.33 (0.15-0.52)	0.001

PCI: placental cord insertion, IHV: intrahepatic vein, IUT: intrauterine transfusion

Discussion

This study demonstrates alterations in brain Doppler flow velocity waveforms in fetuses undergoing intrauterine transfusions for fetal anaemia, in transfusions through the placental cord insertion and the intrahepatic portion of the umbilical vein alike. It has been hypothesized that these changes are an expression of fetal pain (1;3). However, based on our results, it seems unlikely that these alterations are caused by a stress reaction due to a noxious stimulus, as it occurred in both groups and the noxious stimulus was not present in the PCI group.

To our knowledge, there is only one other research group that studied the effect of fetal stress on fetal blood flows. Fisk and his group measured pulsatility indices of the MCA before and after invasive procedures in 44 patients (1;3). In transfusions through the IHV they found a significant decrease in MCA PI whereas in the control PCI group the decrease was not significant. There are previous studies describing similar changes in Doppler flow profiles after intrauterine needling, however as far as we know Fisk was the first to measure these changes specifically in fetuses undergoing invasive procedures involving transgression of the fetal body (6-9).

Compared to Fisk et al. our mean pretransfusion fetal haemoglobin level was lower and we administered a larger amount of blood in each transfusion, with a comparable posttransfusion haemoglobin level. The volume-effect and possibly a related stress-effect was therefore likely larger in our study, potentially masking smaller differences in effect by fetal stress. Another speculation is that severely anaemic fetuses such as in our study group exhibit a less pronounced pain-response as compared to the mildly anaemic fetuses in Fisk's study.

Several authors have described a relationship between volume load and decrease of pulsatility index values(6-9). In our study the decrease in pulsatility index was not correlated to the amount of transfused volume. However, our sample size was probably too small to test this association.

Our routine premedication is indomethacin, pethidin and promethazine. This could have influenced our measurements. However, for indomethacin the mean serum fetal/maternal ratio is 0.95, six hours after oral administration of a 50 mg dose (10). In our study indomethacin 50 mg was administered approximately 30 minutes before the procedure. The maximum effect of pethidin – also administered 30 minutes before the procedure - is reached 3 hours after administration (11). Fetal neuromuscular blockade was achieved with atracurium, which has been shown not to alter fetal heart rate and heart rate variability and is unlikely to influence a pain

response (12). We regard it therefore unlikely that our results are strongly influenced by the medication we administered before and during IUT.

In summary, our results suggest that in anaemic fetuses undergoing transfusion the decrease in MCA PI is caused by other mechanisms than stress, most likely volume expansion.

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