Fetal Pain

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Chapter 5

Placental passage of remifentanil in the second and early third trimester

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Abstract

Introduction Remifentanil, a short-acting opioid, is considered safe and effective for obstetric pain relief and is known to cross the placenta at term. Aim of our study was to determine the placental passage of remifentanil in the second and early third trimester.

Methods Remifentanil was administered intravenously to pregnant women undergoing intrauterine blood transfusions. Remifentanil concentrations were measured in fetal blood samples.

R**esults** Data of 11 transfusions were included. Mean fetal remifentanil concentration was 0.06 (range 0.02-0.19).

Discussion In contrast to findings by others, this study shows a placental passage of remifentanil of only 33%, in the second and early third trimester.

Introduction

There is much debate as to whether a fetus is able to feel pain. The concept of fetal pain will probably remain controversial, simply because we cannot ask the fetus whether or not it feels pain. We can only study indirect evidence of possible harmful effects of stressful stimuli on the developing fetus. There is indeed evidence that some presumably painful fetal procedures or conditions can lead to changes in infant sensitivity [1, 2]. Therefore, to provide some form of fetal analgesia during invasive intrauterine procedures might be beneficial. Remifentanil, a short-acting opioid, is increasingly used for obstetric pain relief, and considered safe for the fetus[3-5]. There is a lack of data on placental passage of remifentanil early in gestation. Aim of our study was to assess placental passage of remifentanil in the second and early third trimester.

Methods

The LUMC is the national referral centre for the treatment of fetal anaemia. Our methods for treatment have been described previously [6].
Women with singleton pregnancies undergoing clinically indicated intrauterine transfusions for fetal red cell alloimmunisation between 19 and 34 weeks were included. Exclusion criteria were morbid obesity, fetal structural anomalies, fetal hydrops or maternal contraindication for remifentanil. Remifentanil was administered by an anaesthesiologist, as continuous infusion with target controlled infusion (TCI) set at 0.2 ng/ml. Infusion was started five minutes before commencing the procedure. All women received indomethacin 50 mg pr half an hour before the procedure to reduce uterine contractility. All fetuses received atracurium (0.4 mg/kg) intravenously immediately after taking the first fetal blood sample. After collection of clinical samples and before commencing the intrauterine transfusion, an additional aliquot of fetal blood was drawn for the assay of remifentanil. The time to access the fetal circulation was recorded in minutes.
All women were part of the NO PAIN study, which we described previously (ClinicalTrials.gov, number NCT01013558) [6]. All women signed written informed consent to the collection of additional samples for research purposes, as approved by the institutional ethics committee.

Data were analysed using GraphPad Prism version 5.00 for Windows, GraphPad Software, San Diego, CA, USA. Statistical analysis was performed using the paired and unpaired t-test and Wilcoxon signed rank test as appropriate. A P-value of <0.05 was considered statistically significant.

Results

Data of 11 transfusions were included. Baseline characteristics are shown in table 1. Gestational ages ranged from 19 to 34 weeks, with a mean gestational age of 29 weeks. Mean time to gaining access to the fetal circulation after entering the maternal abdomen was 4.9 minutes.

Table 1. Baseline characteristics for intrauterine transfusions

	IUT (N=11)
Gestational age at IUT (weeks)	29 (4.6)
Haemoglobin before IUT (g/dl)	7.8 (0.8)
Haemoglobin after IUT (g/dl)	15.2 (0.6)
Mean transfusion volume (ml)	58 (21.9)
Mean transfusion volume (%FPV)	32 (6.8)
Time to access fetal circulation (min)	4.9 (3.2)
Mean duration of IUT (min)	30 (8.9)
EFW at IUT (grams)	1594 (794)

Values are given as mean (SD). IUT: intrauterine transfusion, FPV: fetoplacental blood volume

All women received 0.2 ng/ml remifentanil as TCI, commencing five minutes before the start of the transfusion. Fetal remifentanil concentrations at the start of the transfusion varied between 0.02 and 0.19 ng/ml, with a mean concentration of 0.06 mg/ml. All values are given in table 2.
The mean maternal concentration over mean fetal concentration ratio was 0.2:0.06= 3.3. There was no correlation between gestational age and placental passage of remifentanil in our patient population.

Table 2. Maternal and fetal remifentanil concentration before intrauterine transfusion

		Remifentanil concentration	
	Gestation (weeks)	Maternal (ng/ml)	Fetal (ng/ml)
1	30	0.2	0.02
2	34	0.2	0.02
3	26	0.2	0.02
4	28	0.2	0.02
5	31	0.2	0.19
6	19	0.2	0.08
7	24	0.2	0.05
8	30	0.2	0.05
9	34	0.2	0.11
10	27	0.2	0.04
11	33	0.2	0.02
Mean (SD)	29 (4.6)	0.2 (0)	0.06 (0.05)

SD; standard deviation

Discussion

We calculated a mean maternal concentration over mean fetal concentration ratio of remifentanil of 3.3 during intrauterine transfusions.
As remifentanil has a high speed of onset of effect (1-2 minutes)[7] and we started infusing five minutes before commencing the procedure, it is safe to assume that fetal remifentanil samples were taken after the steady state was reached.
There are several limitations to our study. First, we routinely used indomethacin and atracurium. However, both substances do not interact with remifentanil and therefore we did not expect any influence on our results. Second, the patient population we studied was small which can of course influence the reliability of our results. Third, we aimed to administer 0.15 microgr/kg/min remifentanil to the mother, which corresponds with a plasma concentration of 3.75 ng/ml TCI. This concentration was based on previous work by Van de Velde et al [8]. However, when analysing our data, we discovered that TCI was accidently set at 0.2 ng/ml, which corresponds with 0.008 microgr/kg/min. This is a concentration in which no maternal analgesia is to be expected. As we were analysing the placental passage of remifentanil and not the analgesic effect, this is not a problem; however the lower limit of quantification for remifentanil in the laboratory was 0.2 ng/ml. This means that almost all fetal values were below the lower limit of quantification which makes the results less reliable. Nonetheless, we believe despite this inaccuracy our results clearly suggest that the placental passage of remifentanil in the second and early third trimester is low: at least in the second and early third trimester fetus, the placental passage we measured was only 33%. In contrast, in the term fetus, the placental passage of remifentanil was reported to be 88%[5].
We do not know which concentration of remifentanil is required to achieve fetal analgesia, however we do know from a study of Van de Velde et al that when adequate maternal analgesia is reached, excellent fetal immobilisation is also provided [8]. We are not certain that immobilising the fetus also means that the fetus experiences no stress or pain, but it seems plausible. As the results of our study suggest that the placental passage is only 33% in the second and early third trimester, one could conclude that the fetus would need a lower amount of remifentanil to achieve analgesia as compared to an adult. This is of interest, because children and even newborns require the same amount as adults [9, 10].

Previous studies have investigated the fetal analgesic effect of fentanyl [11]. In these studies, fentanyl was administered directly into the fetal circulation, after puncturing the intrahepatic umbilical vein. Remifentanil can likewise be administered directly into the fetal circulation. However, this would mean losing the benefit of achieving fetal analgesia before administering a painful stimulus to the fetus. Therefore we feel that when it is possible to achieve fetal analgesia transplacentally via the mother, this is a more elegant method. If transplacental fetal analgesia is not available, administering analgesics directly to the fetus remains an option. Further studies should focus on the routes, drugs and dosages that are necessary to achieve fetal analgesia.

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