RIDSTRESS
REDUCING THE RISK OF FETAL DISTRESS WITH SILDENAFIL STUDY

Intrapartum placental transfer of sildenafil citrate in term pregnancies

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Abstract

Introduction - There is limited evidence regarding the extent of fetal transfer of Sildenafil Citrate (SC) in pregnant women in particular when it is administered during labour. The aim of this study was to assess the concentration of SC and its active metabolite N-desmethyl sildenafil (NDS) in maternal blood and umbilical cord blood from women given SC in labour.
Methods –This was a subgroup analysis from a double blind randomised controlled trial assessing the potential of intrapartum oral SC (50mg 8-hourly) compared to placebo for the reduction of intrapartum fetal distress (ACTRN12615000319572). Maternal blood was obtained 1-4 hours after administration of the first dose of SC and cord blood was obtained following delivery, samples were processed and SC and NDS assays performed in Belgium.
Results - Of the 150 participants administered SC, 33 post-treatment maternal samples and 26 cord blood samples were obtained. The median SC concentration in maternal blood was 35.1 (IQR 17.8-63.4) ng/ml 2.6 hours after the first dose of SC treatment whilst the median NDS concentration was 85.2 (45.9-140) ng/ml. At this timepoint the ratio of SC:NDS was 42.2 (27.6-73.7) %. The median SC concentration in cord blood, 5 hours after last dose administration, was 0 (0-24.5) ng/ml and the median NDS concentration was also 0 (0-22.3) ng/ml. The median fetal/maternal concentration ratio of sildenafil was 3.6 (2.6-6.3) %.
Discussion – This study provides reassuring novel evidence that maternal-fetal transfer of SC in labour results in negligible to low levels of SC and NDS in the fetal circulation.

Objectives

Worldwide 23% of the 4-million neonatal deaths per year are as a result of fetal hypoxia occurring gradually due to uterine contractions.
The “Reducing the Incidence of Fetal Distress with Sildenafil Citrate” (**RIDSTRESS**) trial assessed whether administration of sildenafil citrate intrapartum reduced the risk of operative delivery for intrapartum fetal compromise. Sildenafil likely crosses the placenta via passive diffusion. There is limited data available regarding the effects of pregnancy and labour on the pharmacokinetics of oral sildenafil citrate administration as well as on the extent of transplacental transfer intrapartum.

Aim: To determine the levels of sildenafil citrate (SC) and its main metabolite N-desmethyl sildenafil (NDS) in maternal serum and fetal cord blood after intrapartum administration.

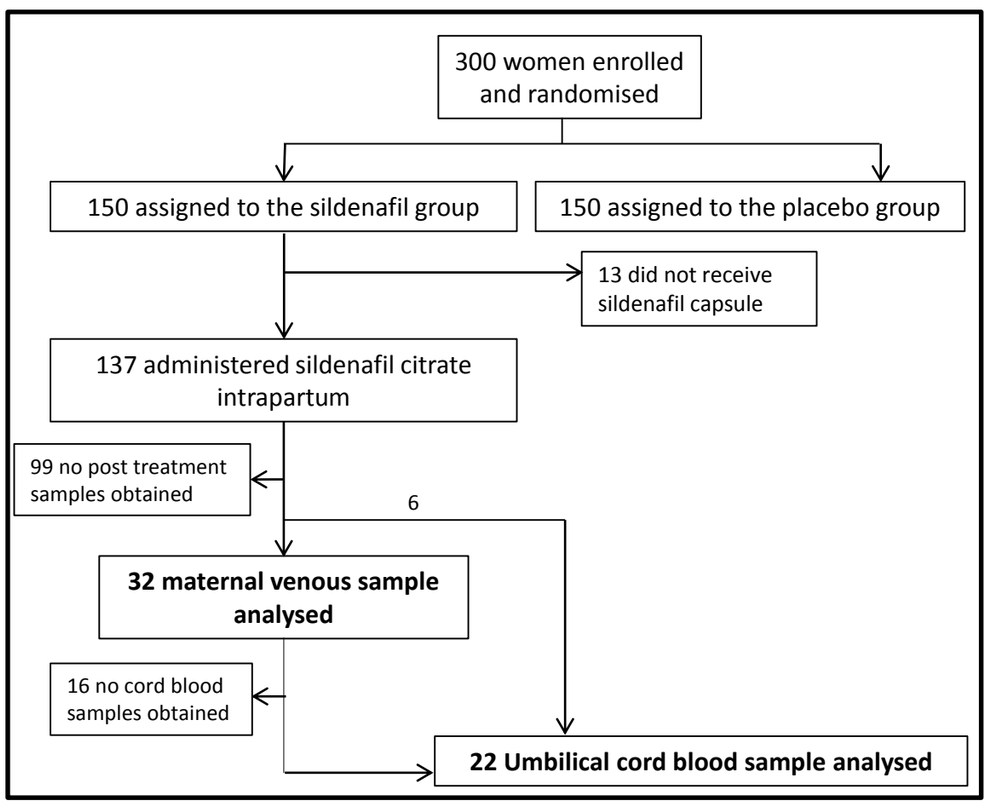
Methods

A sub-group analysis from the **RIDSTRESS trial** *(ANZCTRN12615000319572)*

Participants:
- Women at term in early labour or undergoing scheduled induction of labour at Mater Mother’s Hospital

Study Process:
- Double blind RCT
- Participants randomly assigned 50 mg SC orally 8 hourly to a total of 150mg, or identical placebo in labour
- Maternal blood sample was obtained 1-3hours after the first dose of study medication and cord blood was obtained immediately following delivery
- SC and NDS levels analysed using liquid chromatography spectrometry

Primary outcome: levels of SC and NDS in maternal and fetal cord blood after intrapartum sildenafil administration



Results

	Maternal Sample	Cord Blood sample
n.	32	22
Interval tx - blood test (hrs)	2.6 (1.1)	-
Interval last dose – c.blood (hrs)	-	4.95 (2.7)
Sildenafil citrate (ng/ml)	35.1 (17.8-63.4)	0 (0-11.4)#
N-desmethyl sildenafil (ng/ml)	85.2 (45.9-140)	0 (0-0)#
Ratio NDS:SC (%)	230.2 (135.6-335.6)	61.1 (0-100.5)
Ratio SC fetal:maternal blood	3.6 (2.6-6.3)	
Ratio NDS fetal:maternal blood	1.9 (0.9-2.1)	

*range 0-24.5ng/ml # range 0-22.3

Conclusions

The **key findings** of this study are:
1. Low levels of SC and NDS in umbilical cord blood after intrapartum administration of sildenafil
2. Low ratio of fetal to maternal SC and NDS concentrations

These are significantly lower feto-maternal SC ratios compared to those seen in placental perfusion models of sildenafil transfer and than those seen in neonates treated with SC for pulmonary hypertension (Kelly *et al*).

Limitations:
- small number of participants with paired maternal and cord blood samples.
- Only 1 maternal blood sample per participant

Conclusions: This study suggests that at term, intrapartum sildenafil citrate administration results in low SC concentrations in cord blood at delivery.

References

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