

# Remifentanyl for foetal immobilisation and maternal sedation during endoscopic treatment of twin-to-twin transfusion syndrome : a preliminary dose-finding study

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**Summary :** Twin to twin transfusion syndrome (TTTS) affects 10 to 15% of monochorionic twin pregnancies. Untreated, perinatal loss exceeds 80%, of which survivors have a great risk for long-term neurological disorders as psychomotor retardation or cerebral palsy. TTTS can be treated using foetoscopy and selective ablation of the twin-to-twin blood vessels under local or regional anaesthesia. However, local or regional anaesthesia does not always result in excellent maternal comfort, nor does it provide foetal immobilisation, necessary for optimal surgical conditions.

Using a continuous infusion rate of remifentanyl 0.1 µg/kg/min, perfect foetal immobilisation and excellent maternal sedation was achieved. Only mild respiratory acidosis was observed as a result of mild respiratory depression. In no mother apnoe occurred. All haemodynamic parameters, both foetal and maternal, remained stable during the procedure. Maternal sedation, respiratory depression and foetal immobilisation were quickly reversible following cessation of the remifentanyl infusion.

**Key words :** Twin-to-twin transfusion syndrome ; Foetal surgery ; Remifentanyl ; Foetal immobilisation ; Sedation.

## INTRODUCTION

Twin to twin transfusion syndrome (TTTS) affects 10 to 15% of monochorionic twin pregnancies. Its aetiology remains poorly understood, but basically results from a transplacental vascular communication between the twins, causing blood shunting from the donor to the recipient twin (1). It is defined as presentation in the second trimester with the oligo-polyhydramnios sequence. Using ultrasound, the deepest vertical pool in the donor sac is  $< 2$  cm and  $\geq 8$  cm in the recipient's sac. Other, clinical features are a small or non-visible bladder and abnormal umbilical artery in the donor or a large bladder, cardiac hypertrophy, tricuspid regurgitation, venous overload and eventually

hydrops in the recipient. Untreated, perinatal loss exceeds 80%, of which survivors have a great risk for long-term neurological disorders as psychomotor retardation or cerebral palsy (1, 2).

Advances in high-resolution ultrasound and other diagnostic procedures contribute to early diagnosis and treatment of this severe and life-threatening syndrome.

Miniaturization of existing and available endoscopes has made it possible to treat TTTS using foetoscopy and laser ablation (3). Using this technique, which addresses the underlying pathophysiological mechanism, the inter-twin shunts can be occluded by selective ablation and coagulation of placental vessels.

Initially, selective ablation was performed whilst the mother was under general anaesthesia. In recent years, in most centres this type of procedure is performed under local or regional anaesthesia. This procedure can be performed using local anaesthesia, but in our institution, we prefer the use of combined spinal epidural anaesthesia (CSE) because of possible unsatisfactory maternal anaesthesia with local anaesthesia. Induced polyhydramnios to have a better view and better surgical circumstances is only one reason of maternal discomfort. Furthermore local anaesthetic doses can be considerable thereby introducing the risk of local anaesthetic toxicity.

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Local or regional techniques however are sometimes associated with maternal anxiety. Furthermore, foetal immobilisation is not achieved when mothers remain awake. Mobile foetuses can complicate surgery and prolong the intervention (3). Mobility may lead to displacement of the endoscope resulting in bleeding, foetal trauma or compromised umbilical circulation resulting in foetal death. Even failure to complete the intended surgery could be the result (4).

Remifentanil (ULTIVA®, GSK) is a novel, short acting opioid, which has been used for intra-operative sedation in patients undergoing regional or local anaesthesia (5, 6, 7). In term pregnant women, undergoing elective caesarean section under epidural anaesthesia, it produces excellent maternal sedation without adverse maternal effects. Kan *et al.* demonstrated that a high transplacental passage of remifentanil occurred: MV/UA ratio of 0.8 (8). In the latter study, no adverse foetal or neonatal effects were observed, despite a high transplacental passage of remifentanil.

We hypothesised that remifentanil could produce excellent maternal sedation and foetal immobilisation in second trimester pregnant women undergoing foetoscopy surgery. Therefore we performed a dose-finding study to determine the optimal maternal dose to achieve sedation and immobilisation.

## METHODS

Following institutional Ethics Committee approval and written patient informed consent, 10 healthy (ASA I and II), second trimester pregnant women, carrying a twin and scheduled for endoscopic, intrauterine surgery for TTTS, were included in this dose-finding trial.

Mothers were IV prehydrated using 1000 mL of lactated Ringer's solution through an IV catheter in the right forearm. A second intravenous cannula was positioned in the left antecubital vein to infuse remifentanil. Under local anaesthesia, the left radial artery was cannulated to allow continuous blood pressure measurements and repetitive blood sampling for blood gas analysis.

Combined spinal epidural anaesthesia (CSE) was performed at the L3-L4 or L4-L5 interspace, with the patient in the sitting position. The epidural space was identified using an 18 G Tuohy needle using the loss of resistance to saline technique. The dura was perforated using a 27 G pencil point

spinal needle and 8 mg of hyperbaric bupivacaine was injected into the spinal space, after which a 20 G epidural catheter was advanced 4 cm into the epidural space. Anaesthesia was maintained by additional epidural top-ups of ropivacaine 0.75% at the discretion of the attending anaesthesiologist.

The patient was then positioned in the supine position with left lateral tilt to prevent aortocaval compression. Supplemental oxygen (5 litres) was routinely administered by facemask to optimise foetomaternal oxygenation status. Following baseline recordings, maternal IV sedation was started.

Remifentanil infusion was started if spinal analgesia reached the fourth thoracic dermatome. This was tested as anaesthesia to cold (ether). The initial infusion rate was 0.025 µg/kg/minute, and this was raised by 0.025 µg/kg/minute every 20 minutes until 0.1 µg/kg/minute. If maternal respiratory rate (RR) decreased below 8 times/minute or if maternal arterial pH decreased below 7.30, remifentanil was decreased by 0.025 µg/kg/min.

Foetal heart rate (FHR) was recorded every 15 minutes using ultrasound.

Foetal immobility was assessed by the obstetrician, performing the intra-operative ultrasound. He scored foetal mobility prior to the start of sedation and every 20 minutes during surgery, using a VAS score (MOV VAS 0 = immobile foetus, 100 = extremely mobile foetus). Maternal blood pressure was measured in the radial artery and expressed as mean arterial blood pressure. Maternal RR was measured. Maternal heart rate was recorded. Maternal sedation was expressed as a VAS score (VAS sed 0 = no sedation, 100 = unresponsive) and the observer alertness score (OAA/S) by the attending anaesthesiologist unaware of the remifentanil dose infused.

Maternal blood gases were determined at baseline and during surgery at regular time intervals.

Data were analysed using one-way repeated measures ANOVA. When significant differences were observed, student's *t* test for post hoc testing was used.

Data are presented as mean ± standard deviation. A *p* < 0.05 was considered statistically significant.

## RESULTS

All 10 patients completed the study. Demographic data, pregnancy duration, duration of

Table I

Age, weight, height, pregnancy duration (PML), duration of surgery (T<sub>urg</sub>), mean remifentanyl dose (R<sub>dose</sub>), mean infusion rate (I<sub>rate</sub>)

Age (years)	29,1 ± 5,6
Weight (kg)	73 ± 16
Height (cm)	163 ± 7
PML (weeks)	20,6 ± 3,4
T <sub>urg</sub> (minutes)	111 ± 32
R <sub>dose</sub> (µg)	289 ± 21
I <sub>rate</sub> (µg/kg/')	0,0668 ± 0,0218

Data are presented as mean ± Standard Deviation.

surgery, mean remifentanyl dose and mean remifentanyl infusion rate are presented in table I.

FHR remained stable throughout the surgical procedure and was not influenced by the remifentanyl infusion rate or cumulative dose (Table II). Foetal mobility was largely influenced by the remifentanyl infusion rate. A MOV VAS of 89 ± 13 at baseline gradually decreased to 0 ± 0 at an infusion rate of 0.1 µg/kg/min, but returned to baseline values within 30 minutes after the infusion was stopped (Fig. 1).

Maternal sedation increased from VAS sed O at baseline to 47 ± 12 at an infusion rate of 0.1 µg/kg/min. Using the OAA/S, all ten women had OAA/S values of 5 and 6 at baseline. At an infusion rate of 0.1 µg/kg/min, all ten women had

Table II

Maternal and foetal heart rate (MHR and FHR), maternal mean arterial pressure (MmABP), maternal pO<sub>2</sub> (MpO<sub>2</sub>), maternal saturation (MSAT) before, during and after remifentanyl infusion

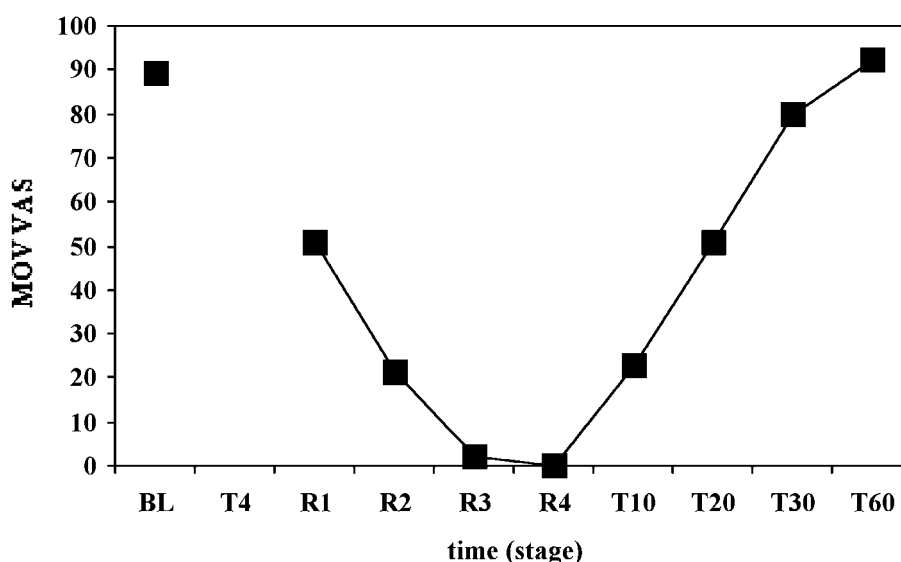
	MHR (bpm)	FHR (bpm)	MmABP (mm Hg)	MpO <sub>2</sub> (mm Hg)	MSAT (%)
BL	91 ± 16	142 ± 8	91 ± 7	137 ± 18	98 ± 1
T4	98 ± 15	141 ± 8	82 ± 12	124 ± 40	99 ± 1
R1	94 ± 15	146 ± 13	85 ± 12	217 ± 29	100 ± 1
R2	90 ± 15	148 ± 11	90 ± 5	212 ± 27	100 ± 1
R3	97 ± 17	150 ± 11	86 ± 8	187 ± 46	99 ± 1
R4	91 ± 9	144 ± 10	85 ± 11	200 ± 28	99 ± 1
T10	99 ± 11	143 ± 9	85 ± 8	187 ± 35	99 ± 1
T30	91 ± 7	142 ± 7	85 ± 7	164 ± 45	99 ± 1
T60	86 ± 16	138 ± 8	84 ± 7	132 ± 12	99 ± 1

BL : baseline ; T4 : dermatomal level T4 ; R1 : remifentanyl 0.025 µg/kg/'; R2 : remifentanyl 0.050 µg/kg/'; R3 : remifentanyl 0.075 µg/kg/'; R4 : remifentanyl 0.1 µg/kg/'; T10 : 10 minutes after cessation of remifentanyl ; T30 : 30 minutes after cessation of remifentanyl ; T60 : 60 minutes after cessation of remifentanyl.

Data are presented as mean ± Standard Deviation.  
No statistical significant changes were identified.

an OAA/S of 3 or 4. Twenty minutes after surgery, all ten women recovered and had an OAA/S of more than 4 (Table III, Fig. 2).

Maternal HR and mABP remained stable during surgery and at any given remifentanyl infusion rate (Table II). All mothers tended to hypoventilate during remifentanyl infusion. Maternal respiratory rate decreased from 18.8 ± 3.2 times per minute at



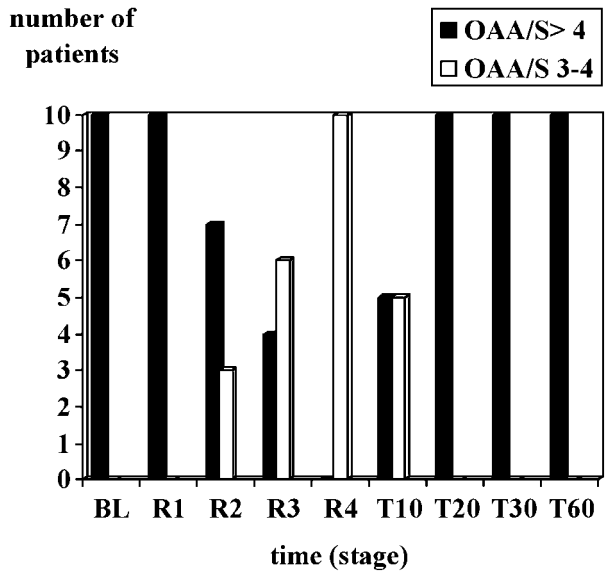
BL : baseline ; T4 : dermatomal level T4 ; R1 : remifentanyl 0.025 µg/kg/'; R2 : remifentanyl 0.050 µg/kg/'; R3 : remifentanyl 0.075 µg/kg/'; R4 : remifentanyl 0.1 µg/kg/'; T10 : 10 minutes after cessation of remifentanyl ; T30 : 30 minutes after cessation of remifentanyl ; T60 : 60 minutes after cessation of remifentanyl.

Values at R1, R2, R3, R4, T10 and T20 are statistically significant versus BL : p < 0,05.

Fig. 1. — MOV VAS scores of foetuses before, during and after remifentanyl infusion.

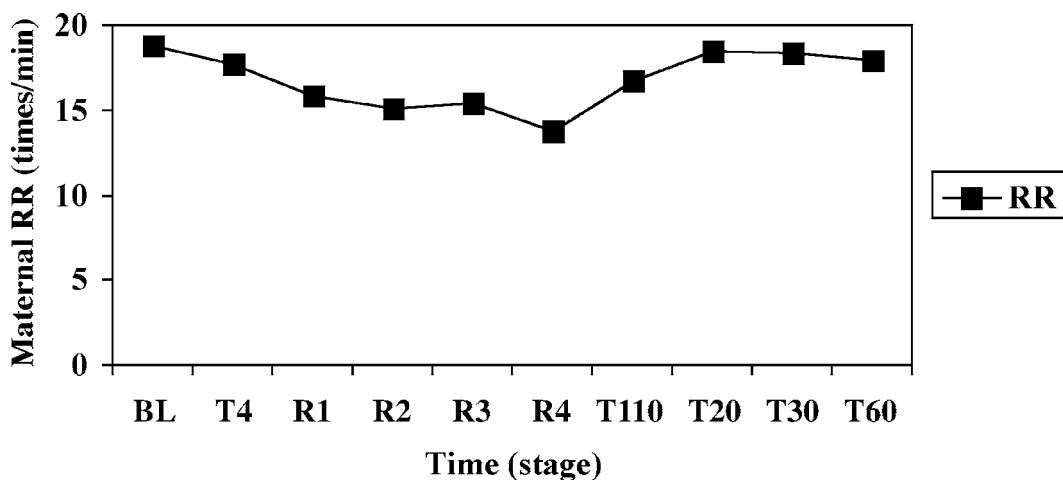
*Table III*  
The observer alertness score (OAA/S)

6	Patient is awake and anxious
5	Patient is awake but does not feel anxious
4	Patient sleeps, but can easily be aroused by verbal stimuli
3	Patient sleeps and can easily be aroused by mild physical contact
2	Patient sleeps and can only be aroused by firm physical contact
1	Patient is unresponsive



BL : baseline ; T4 : dermatomal level T4 ; R1 : remifentanyl 0.025 µg/kg/'; R2 : remifentanyl 0.050 µg/kg/'; R3 : remifentanyl 0.075 µg/kg/'; R4 : remifentanyl 0.1 µg/kg/'; T10 : 10 minutes after cessation of remifentanyl ; T30 : 30 minutes after cessation of remifentanyl ; T60 : 60 minutes after cessation of remifentanyl.

Fig. 2. — OAA/S scores of mothers before, during and after remifentanyl infusion.



BL : baseline ; T4 : dermatomal level T4 ; R1 : remifentanyl 0.025 µg/kg/'; R2 : remifentanyl 0.050 µg/kg/'; R3 : remifentanyl 0.075 µg/kg/'; R4 : remifentanyl 0.1 µg/kg/'; T10 : 10 minutes after cessation of remifentanyl ; T30 : 30 minutes after cessation of remifentanyl ; T60 : 60 minutes after cessation of remifentanyl.

No statistically significant differences have been found.

Fig. 3. — Maternal respiratory rate before, during and after remifentanyl infusion

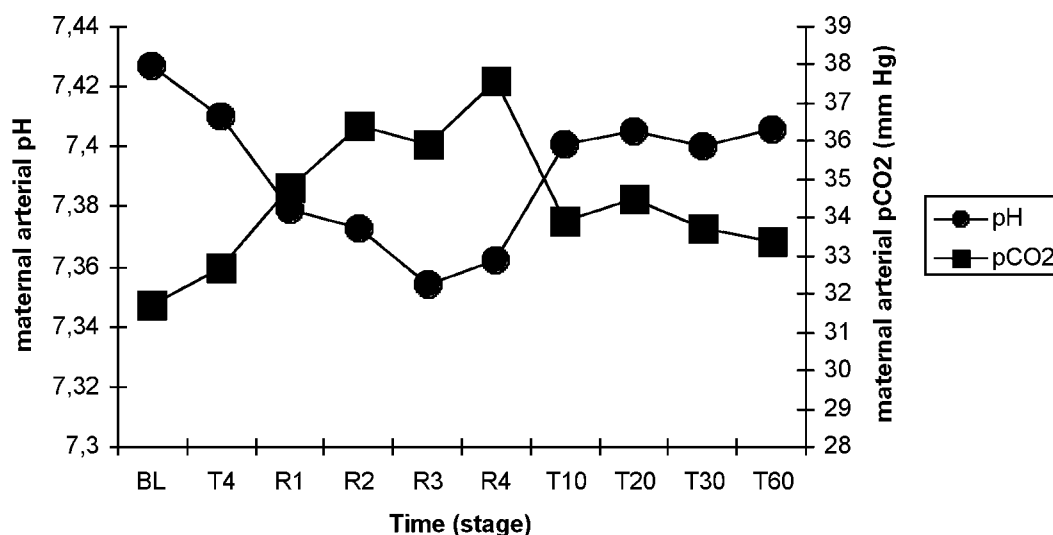
baseline to  $13.8 \pm 2.5$  times per minute at an infusion rate of  $0.1 \mu\text{g/kg/min}$  (Fig. 3). As a result, maternal arterial pCO<sub>2</sub> increased from  $31.7 \pm 2.7$  mm Hg to  $37.6 \pm 5.9$  mm Hg and arterial pH decreased from  $7.427 \pm 0.019$  to  $7.362 \pm 0.046$  (Table IV, Fig. 4). In no mother the RR decreased below 8 times per minute during surgery.

Maternal oxygen saturation and pO<sub>2</sub> did not change during surgery, using a facemask and providing 5 litres of oxygen per minute (Table II).

DISCUSSION

Maternal remifentanyl infusion produced excellent and easily reversible foetal immobilisation and maternal sedation without foetal complications and only minimal maternal respiratory depression, which was clinically insignificant. A dose of  $0.1 \mu\text{g/kg/minute}$  seems to be the optimal dose resulting in perfect foetal immobility and adequate maternal sedation.

Remifentanyl has a high transplacental passage (8) : an UV/MA ratio of 0.88, which is higher than that of most other synthetic opioids. Alfentanil has an UV/MA ratio of 0.3 ; the ratio of fentanyl varies between 0.37 and 0.57. Only the ratio of sufentanyl (0.81) is similar to that of remifentanyl. Intravenously administered fentanyl or sufentanyl also produce foetal immobility and reduce foetal heart rate variability. It is therefore not surprising that also remifentanyl successfully reduced foetal



BL : baseline ; T4 : dermatomal level T4 ; R1 : remifentanil 0.025  $\mu\text{g}/\text{kg}/\text{min}$  ; R2 : remifentanil 0.050  $\mu\text{g}/\text{kg}/\text{min}$  ; R3 : remifentanil 0.075  $\mu\text{g}/\text{kg}/\text{min}$  ; R4 : remifentanil 0.1  $\mu\text{g}/\text{kg}/\text{min}$  ; T10 : 10 minutes after cessation of remifentanil ; T30 : 30 minutes after cessation of remifentanil ; T60 : 60 minutes after cessation of remifentanil.

No statistically significant differences were identified.

Fig. 4. — Maternal pH and pCO<sub>2</sub> before, during and after remifentanil infusion

Table IV

VAS sedation scores of mothers before, during and after remifentanil infusion

Time	VAS sed
BL	0 ± 0
T4	0 ± 0
R1	21 ± 18
R2	30 ± 20
R3	44 ± 15
R4	47 ± 12
T10	11 ± 19
T20	6 ± 14
T30	4 ± 8
T60	0 ± 0

Data are presented as mean ± Standard Deviation.

\*  $p < 0.05$  versus base line.

BL : baseline ; T4 : dermatomal level T4 ; R1 : remifentanil 0.025  $\mu\text{g}/\text{kg}/\text{min}$  ; R2 : remifentanil 0.050  $\mu\text{g}/\text{kg}/\text{min}$  ; R3 : remifentanil 0.075  $\mu\text{g}/\text{kg}/\text{min}$  ; R4 : remifentanil 0.1  $\mu\text{g}/\text{kg}/\text{min}$  ; T10 : 10 minutes after cessation of remifentanil ; T30 : 30 minutes after cessation of remifentanil ; T60 : 60 minutes after cessation of remifentanil.

movements. Because of its high transplacental passage, short duration of action and titrability, we preferred to use remifentanil for sedation and foetal immobilisation during awake foetoscopic surgery as opposed to other opioids.

Using an infusion rate of 0.1  $\mu\text{g}/\text{kg}/\text{min}$ , maternal sedation was excellent. All mothers had an OAA/S of 3 or 4, which means that the patient sleeps, but can be easily aroused by verbal stimuli or by mild physical contact. Importantly, no

woman had an OAA/S of less than 3. Thus maternal sedation was adequate and no episodes of profound sedation were observed. Ten minutes after discontinuation of the remifentanil infusion, half of all the mothers had an OAA/S more than 4. And after twenty minutes, all mothers had recovered well from the opioid infusion. As expected maternal sedation was short-lived and allowed rapid recovery and discharge from the recovery area.

Maternal remifentanil infusion resulted in maternal hypoventilation. Although maternal respiratory acidosis occurred, it was mild and did not result in signs of foetal distress. More importantly, remifentanil did not result in apnoea ! These results are in line with previous studies by Babenco et al, who determined the respiratory effects of a remifentanil bolus in healthy volunteers. A bolus produced short lasting hypoventilation without respiratory arrest. (9) Importantly maternal respiratory rate and maternal blood gas values quickly returned to baseline levels within twenty minutes following cessation of the remifentanil infusion.

The present trial did not evaluate doses above 0.1  $\mu\text{g}/\text{kg}/\text{min}$  because of the limited duration of surgery. However, since 0.1  $\mu\text{g}/\text{kg}/\text{min}$  produced complete foetal immobility and adequate maternal sedation, we feel no additional advantages can be expected from increasing the infusion rate.

It is important to stress that surgery was performed on the placenta and not on the foetus. It is highly likely that remifentanil in a dose of

0.1 µg/kg/minute is completely insufficient to provide foetal anaesthesia during surgery associated with direct foetal trauma. However, this limited dose did provide excellent foetal immobility for this type of intervention and improved surgical exposure and contributed to safe and effective surgery.

The primary goals of the present trial were to evaluate the maternal and foetal effects of intravenous remifentanyl in second trimester pregnant women undergoing foetoscopy of the placenta and to determine the optimal dose for foetal immobilisation and maternal sedation. From this trial we can conclude that the use of remifentanyl during foetal endoscopic surgery is safe and has no clinically important side effects on the mother or the foetus, except mild maternal acidosis, which quickly recovers following cessation of the remifentanyl infusion. At present a dose of 0.1 µg/kg/minute can be recommended. Currently we are performing a randomised trial comparing remifentanyl with other forms of maternal sedation during foetoscopy surgery.

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