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The effect of ketamine anaesthesia on the acidotic fetal lamb

The following study in pregnant ewes was done to examine the effects of ketamine-oxygen anaesthesia on the fetal lamb made acidotic by partial occlusion of the umbilical cord.

Fifteen pregnant ewes were instrumented under general anaesthesia to allow continuous measurement of maternal and fetal mean arterial pressure and pulse rate and for withdrawal of arterial blood samples for blood gas analysis. An occlusion loop was loosely secured around the umbilical cord.

Following a recovery period of 48 hours, a tracheostomy was performed on each ewe. After a control period, the umbilical occlusion loop was slowly inflated until fetal pH had decreased to 7.12–7.15. Following inflation the animals were divided into groups A and B. Group A received no anaesthesia. In Group B, the ewes received ketamine $3 \text{ mg} \cdot \text{kg}^{-1}$ intravenously and controlled ventilation with FiO_2 of 1.0. After ten minutes ketamine $1 \text{ mg} \cdot \text{kg}^{-1}$ was given. In both groups radioactive microspheres were injected into the fetus at 0, 5, and 15 minutes.

Ketamine anaesthesia in the pregnant ewe abolished the fetal hypertension and bradycardia produced by partial cord occlusion. All fetuses survived the 15 minutes of ketamine anaesthesia and there were no significant changes in arterial blood gases or pH. Blood flows determined by the microsphere method to the brain, heart, and kidneys were not significantly altered by ketamine. We conclude that ketamine-oxygen anaesthesia does not cause further deterioration in the acidotic fetal lamb.

Key words

ANAESTHESIA: obstetric; ANAESTHETICS, INTRAVENOUS: ketamine; FETUS: acidosis.

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The degree of fetal acidosis and the effects of anaesthetic agents on the stressed fetus are difficult to quantitate clinically.¹ However, the presence of fetal distress may necessitate expeditious delivery, often by Caesarean section under general anaesthesia. The best combination of anaesthetic agents remains to be determined.

Previous work from our laboratory suggests that in the severely asphyxiated fetus blood pressure and cerebral blood flow may be better preserved using ketamine rather than thiopentone for induction of anaesthesia.² The advantages of ketamine in this setting are its rapid onset of action and its potent analgesic and amnesic properties. Ketamine allows the administration of 100 per cent oxygen to the parturient and provides haemodynamic stability.

In previous studies we have used a model of fetal asphyxia involving partial occlusion of the umbilical cord to document the haemodynamic and acid-base changes that occur with time.^{3,4} The purpose of this present study was to examine the haemodynamic effects of ketamine: oxygen anaesthesia on the asphyxiated fetal lamb in comparison with a non-anaesthetized control group.

Methods

Consent for this protocol was obtained from the Animal Care Committee of the University of Manitoba. Fifteen pregnant ewes of 125–135 days gestation (term 150 days) were surgically prepared as previously described.⁵ Briefly, under general anaesthesia polyvinyl catheters were placed in the maternal femoral artery and vein. Via a hysterotomy incision, polyvinyl catheters were placed in the fetal femoral artery and vein and brachial artery. An occlusion loop was secured loosely around the umbilical cord and the hysterotomy incision closed. All animals were allowed to recover for 48–72 hours following surgery. No animal was included in the study unless fetal arterial PO_2 was greater than 15 torr and pH was greater than 7.30. On the day of study a maternal tracheostomy was performed under halothane: oxygen mask anaesthesia. Lidocaine two per cent 5 cc was injected into the trachea with insertion of the tracheostomy tube. Each animal was allowed to recover for a minimum of one hour breathing humidified oxygen at a rate of 15 litres per minute. The tracheostomy was done to avoid diffi-

TABLE 1 Maternal pulse rate and blood pressure in the control group (A) and the ketamine:O₂ anaesthesia group (B) during control period, production of fetal acidosis and with general anaesthesia (mean $\pm$ SEM)

	Control		Fetal acidosis (pH 7.12–7.13)	Fetal acidosis plus anaesthesia (Group B)	
	15 min	30 min		5 min	15 min
<i>Pulse rate</i>					
Group A n = 7	95 $\pm$ 7.6	92 $\pm$ 7.9	92 $\pm$ 9.0	91 $\pm$ 8.7	88 $\pm$ 9.5
Group B n = 8	100 $\pm$ 5.7	100 $\pm$ 4.6	100 $\pm$ 5.2	98 $\pm$ 4.7	100 $\pm$ 5.1
<i>Mean arterial blood pressure (MABP)</i>					
Group A n = 7	84 $\pm$ 3.7	82 $\pm$ 3.4	80 $\pm$ 4.7	80 $\pm$ 5.5	81 $\pm$ 3.2
Group B n = 8	96 $\pm$ 7.0	96 $\pm$ 4.4	89 $\pm$ 4.7	103 $\pm$ 5.5*	100 $\pm$ 5.0*

*p < 0.05 compared to Group A at 5 and 15 minutes.

culties with airway instrumentation during the anaesthesia portion of the study.

During each study maternal and fetal mean arterial blood pressure (MABP) and pulse rates were recorded continuously on a Hewlett-Packard multi-channel recorder. Blood samples were obtained from the maternal femoral artery and the fetal brachial artery for pH and blood gas analysis at 15-minute intervals or more frequently as required during asphyxia. Fetal blood losses were replaced with normal saline.

Each study began with a control period of 30 minutes to ensure stability of the preparation. The ewe breathed humidified oxygen at a flow rate of 15 litres per minute via the tracheostomy and received a volume load of 500 ml of normal saline followed by an infusion of 150 ml·hr⁻¹. At the conclusion of the control period the umbilical cord occlusion loop was gradually inflated until fetal pH was 7.12–7.15. This usually required 90 minutes.

When this pH range was obtained the first injection of radioactive chromium, cerium, or strontium labelled microspheres (diameter 10 micron, 3M Company, Minneapolis) was made. This technique has previously been described.⁵

Following the first microsphere injection the animals were randomly assigned to one of two groups. Group A (n = 7) received no anaesthesia and served as the control group. Ewes in Group A continued to breathe humidified oxygen at 15 L·min⁻¹ for 15 minutes. Repeat microsphere injections were made at 5 and 15 minutes. Group B (n = 8) received ketamine 3 mg·kg⁻¹ intravenously via the maternal femoral vein catheter for induction of anaesthesia. A second dose of ketamine 1 mg·kg⁻¹ was administered at ten minutes postinduction to maintain anaesthesia for the duration of the study period. All animals received 100 per cent oxygen and ventilation was controlled to maintain a normal PCO₂. In both groups the occlusion

loop remained inflated for the duration of the study. The second and third microsphere injections were made at 5 and 15 minutes following induction of anaesthesia.

After the third microsphere injection all animals were killed with an injection of thiopentone, followed by KCl. The fetuses were removed, weighed, and dissected. The fetal brain, heart, and kidneys were separately weighed, ground, and ashed. Microsphere counts were performed on these samples and the counts were compared with the reference blood samples to calculate organ blood flow.⁶ Blood flow to the right and left kidneys were calculated separately to serve as a marker for even distribution of microspheres to all organs. Discrepancy between right and left kidney flow suggests uneven mixing of the microspheres.

Statistical analysis

Maternal and fetal MABP, pulse rate, blood gases, pH and organ blood flows were subjected to analysis of variance for repeated measures to detect significant changes within groups. Intergroup comparisons were performed by the unpaired Student's t test. A p value < 0.05 was considered statistically significant.

Results

Maternal changes (Table 1)

There were no significant changes in the maternal pulse rate, PCO₂, or base excess (BE) in either group during the study. Maternal arterial PO₂ in both groups was 195–230 mmHg during the control period and during the time when fetal acidosis was being produced. In Group B, with anaesthesia and controlled ventilation maternal PO₂ rose significantly to 306 $\pm$ 37.3 mmHg and remained above 300 mmHg for the duration of the ketamine anaes-

TABLE II Fetal pulse rate, blood pressure, and blood gases in the control group (A) and the ketamine:O₂ anaesthesia group (B) during control period, production of acidosis and with general anaesthesia (mean $\pm$ SEM)

	Control		Fetal acidosis (pH 7.12–7.13)	Acidosis plus anaesthesia (Group B)	
	15 min	30 min		5 min	15 min
Pulse rate					
Group A	146 ± 4.9	148 ± 6.3	123 ± 13.1†	113 ± 9.2‡	105 ± 16.3†
Group B	146 ± 5.0	153 ± 2.5	133 ± 11.8†	171 ± 15.0†‡	166 ± 14.7†‡
Mean arterial blood pressure (MABP)					
Group A	54 ± 3.9	55 ± 2.5	72 ± 5.8†	73 ± 5.0‡	66 ± 8.5†
Group B	56 ± 3.1	58 ± 3.0	71 ± 6.0†	61 ± 5.5	56 ± 5.4
pH					
Group A	7.34 ± 0.02	7.36 ± 0.03	7.12 ± 0.01†	7.09 ± 0.02†	7.02 ± 0.02†
Group B	7.41 ± 0.01	7.42 ± 1.01	7.13 ± 1.02‡	7.08 ± 0.02†	7.07 ± 0.02†
PCO ₂ (mmHg)					
Group A	40 ± 1.8	40 ± 1.8	57 ± 2.7†	58 ± 1.9†	70 ± 7.1*†
Group B	37 ± 1.3	34 ± 0.8	48 ± 14.7†	53 ± 4.1†	58 ± 3.6†
PO ₂ (mmHg)					
Group A	25 ± 2.4	23 ± 2.4	20 ± 2.2	20 ± 2.6	17 ± 1.3
Group B	21 ± 1.1	19 ± 1.2	19 ± 1.8	22 ± 2.5	20 ± 3.2

*p < 0.05 compared to asphyxia values in the same group.

†p < 0.05 compared to control values in the same group.

‡p < 0.05 compared to Group A at 5 and 15 minutes.

thetia. Maternal pH decreased significantly in Group B from 7.52 ± 0.03 during control to 7.47 ± 0.03 prior to anaesthesia. After 15 minutes of anaesthesia the maternal pH was 7.44 ± 0.04 . However the pH in Group B was not significantly different from the pH in Group A at any time during the study.

Production of fetal asphyxia (Table II)

Inflation of the umbilical occlusion loop over a 60–90 minute period resulted in a statistically significant decrease in fetal pH to a range of 7.12–7.13. Fetal MABP increased from a range of 54–58 to 71–72 mmHg and pulse rate decreased from 146–153 to 123–133 beats·min⁻¹. These measurements were significantly different from control in both groups and persisted for the duration of the study in the nonanaesthetized Group A. There were no changes in fetal PO₂ measured from the brachial artery in either group during the production of acidosis or during anaesthesia. Fetal PCO₂ rose significantly from 37–40 mmHg prior to cord occlusion to 48–57 mmHg with acidosis. Base excess decreased significantly from -2.4 to -0.4 to -10 to -13 in the two groups.

Fetal effects of ketamine anaesthesia (Table II)

Group A: This group received no anaesthesia. There were no further changes in MABP, pulse rate, blood gases or pH.

Group B: Induction of anaesthesia with ketamine 3 mg·kg⁻¹ in the ewe abolished the fetal hypertensive response to acidosis with a significant fall in MABP from 71 ± 6.0 mmHg to 61 ± 5.5 mmHg. Ketamine anaesthesia also resulted in fetal tachycardia with an increase in pulse rate from 133 ± 12 to 171 ± 15 beats·min⁻¹ within five minutes. This persisted for the duration of the study. This increase was significant when compared to values just prior to induction of anaesthesia and to values at 5 and 15 minutes in Group A. There were no significant changes in blood gases or pH.

FETAL BLOOD FLOWS (Table III)

Total cerebral blood flow was in the range of 2.87–3.87 ml·g⁻¹·min⁻¹ in both groups A and B following production of fetal acidosis. There were no significant differences between the two groups at the 5 and 15 minute measurements. There were also no significant differences between the groups in myocardial or renal blood flow. Right and left renal blood flow were similar indicating equal distribution of microspheres.

Discussion

Perinatal asphyxia may result in permanent neurological sequelae in the newborn.^{7,8} The mechanism of injury to the central nervous system appears to depend primarily on abnormal cerebral perfusion. Acidosis and asphyxia

TABLE III Organ blood flows ($\text{ml} \cdot \text{g}^{-1} \cdot \text{min}^{-1}$) just prior to, and after 5 and 15 minutes of anaesthesia* (mean $\pm$ SEM)

		<i>Acidosis</i>		<i>5 Minutes</i>		<i>15 Minutes</i>	
<i>Brain</i>							
Group A		3.87 ± 0.36		3.69 ± 0.45		3.12 ± 0.75	
n = 7							
Group B		2.87 ± 0.68		2.30 ± 0.68		3.03 ± 0.90	
n = 8							
<i>Heart</i>							
Group A		2.47 ± 0.61		1.70 ± 0.31		2.34 ± 0.40	
Group B		1.39 ± 0.23		1.51 ± 0.35		1.90 ± 0.56	
<i>Renal</i>	<i>R</i>	<i>L</i>	<i>R</i>	<i>L</i>	<i>R</i>	<i>L</i>	
Group A	0.67 ± 0.10	0.67 ± 0.09	0.59 ± 0.08	0.61 ± 0.09	0.51 ± 0.13	0.56 ± 0.15	
Group B	0.59 ± 0.14	0.69 ± 0.18	0.62 ± 0.09	0.69 ± 0.24	0.73 ± 0.22	0.85 ± 0.30	

*Anaesthesia in Group B only.

result in a pressure passive cerebral vasculature with loss of auto-regulation of cerebral perfusion in response to changes in blood pressure.^{3,9,10} The asphyxiated fetus or newborn is then exposed to two potential hazards: hypotension with resultant cerebral ischaemia or hypertension with increased risk of intracerebral haemorrhage.

Umbilical cord compression produces both respiratory and metabolic acidosis in the fetal lamb. Cardiac output is severely reduced due to decreased venous return. Gas exchange is impaired due to reduced flow to the placenta. Acidosis shifts the oxyhaemoglobin dissociation curve to the right with desaturation of haemoglobin and reduction of oxygen content.² In response to acidosis and hypovolaemia, fetal blood pressure increases in an attempt to maintain perfusion and oxygen supply to vital organs such as the brain and heart. This increase in MABP is due to peripheral vasoconstriction mediated via the sympathetic nervous system.¹¹ The decrease in pulse rate implies an intact baroreceptor response to hypertension. As previously reported, the consistently increased cerebral blood flow seen in this sheep model represents attempts by the fetus to maintain oxygen supply to the brain in the face of hypovolaemia and reduced oxygen content.³

Induction of anaesthesia with ketamine in Group B abolished the hypertension and bradycardia produced by cord occlusion. The increase in heart rate was unable to compensate for the loss of the vasoconstrictor response, however, and fetal MABP dropped significantly. These results are similar to our previous findings using thiopentone for anaesthetic induction and halothane:oxygen or halothane:nitrous oxide:oxygen for maintenance of anaesthesia.⁵ However, in those experiments, fetal MABP fell to values significantly below the MABP in the control asphyxiated but unanaesthetized fetuses. In the present study, ketamine anaesthesia resulted in a 20 per cent

fall in fetal MABP. The MABP range in both groups was wide, however, so no significant difference between Groups A and B was observed. All fetuses survived the 15-minute post-asphyxia period under anaesthesia and despite the fall in fetal MABP cerebral and myocardial perfusion were maintained.

Other authors have shown that ketamine does not reduce uterine blood flow at a dose of $5 \text{ mg} \cdot \text{kg}^{-1}$ in the pregnant ewe.¹² These investigators demonstrated that uterine blood flow increased concomitantly with increased cardiac output and maternal blood pressure following ketamine administration. Uterine tone has been shown to increase in the pregnant ewe following low dose ketamine ($0.7 \text{ mg} \cdot \text{kg}^{-1}$) but in the same study, uterine blood flow was maintained secondary to increased cardiac output.¹³ Low-dose ketamine ($0.6\text{--}1 \text{ mg} \cdot \text{kg}^{-1}$) administered to pregnant women at term does not increase resting uterine tone.¹⁴⁻¹⁶ Ketamine administered to the term parturient in doses greater than $1.0 \text{ mg} \cdot \text{kg}^{-1}$ may increase the intensity of uterine contractions.¹⁶ Although it is difficult to extrapolate from animal studies to the clinical situation, one may speculate that uterine and feto-placental perfusion are well maintained following ketamine anaesthesia in the parturient with an adequate intravascular blood volume.

When fetal asphyxia is severe the time from diagnosis to delivery is an important factor in determining survival. Fetal compensatory mechanisms ultimately fail at some critical point with resultant demise. In this study we observed that ketamine anaesthesia abolishes the compensatory mechanisms of hypertension and bradycardia seen with partial cord occlusion. Nevertheless, with severe acidosis ($\text{pH} < 7.15$), ketamine anaesthesia does not produce significant deterioration in fetal blood gases, pH, or in cerebral and myocardial blood flow.

Ketamine has been recommended as an alternative

anaesthetic induction agent to thiopentone for elective Caesarean section.¹⁷⁻¹⁹ The clinical situation of severe fetal distress may necessitate a general anaesthetic and there may be insufficient time for a regional technique. Our current findings corroborate the results of previous studies and suggest that ketamine is a safe anaesthetic agent in acute fetal distress.

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Résumé

La présente étude fut faite sur des brebis pleines afin d'examiner les effets de l'anesthésie à la kétamine-oxygène sur le fœtus de la brebis rendu acidotique par occlusion partielle du cordon ombilical.

Quinze brebis pleines étaient instrumentées sous anesthésie générale afin de permettre la mesure continue de la pression artérielle moyenne maternelle et fœtale ainsi que la mesure du pouls et l'étude de la gazométrie. Un tourniquet permettant l'occlusion fut installé autour du cordon ombilical.

Après une période de recouvrement de 48 heures une trachéostomie fut faite pour chaque brebis. Après une période de contrôle l'occlusion du cordon ombilical fut accomplie lentement jusqu'à la diminution du pH fœtal à 7.12-7.15. Après l'occlusion les animaux furent divisés en deux groupes A et B. Le groupe A n'a reçu aucune anesthésie. Dans le groupe B, les brebis ont reçu de la kétamine 3 mg·kg⁻¹ par voie intraveineuse et leur ventilation fut contrôlée avec une FiO₂ de 1.0. Dix minutes plus tard de la kétamine 1 mg·kg⁻¹ fut donnée. Dans les deux groupes des microsphères radioactives furent injectées dans le fœtus à 0, 5, et 15 minutes.

L'anesthésie à la kétamine chez les brebis pleines a aboli l'hypertension et la bradycardie produite par l'occlusion partielle du cordon ombilical chez les fœtus. Tous les fœtus ont survécu les 15 minutes de l'anesthésie à la kétamine et il n'y avait aucun changement significatif des gaz sanguins artériels ou du pH. Les flots sanguins déterminés par la méthode des microsphères pour le cerveau, cœur et reins ne furent pas significativement altérés par la kétamine. On conclut que l'anesthésie à la kétamine-oxygène n'amène pas l'avantage de détérioration chez le fœtus acidotique des brebis.