Ephedrine In Obstetrics? The Clinical Data Say No!

Edward T Riley, MD, Associate Professor
Department of Anesthesia
Stanford University School of Medicine

Introduction

The story of the use of ephedrine in obstetric anesthesia is a perfect example of why clinical research is necessary even when the laboratory and animal data clearly demonstrate a drug’s superiority. In the case of ephedrine in obstetrics, there is overwhelming animal evidence that it is safer for the fetus than any other pressor and there is even laboratory data that describes a mechanism for why this would be the case. The problem is that there is no clinical evidence that ephedrine is actually superior to other pressors in obstetrics. In fact, there is plenty of clinical data that suggests the opposite; ephedrine may be harmful for the fetus.

Historical Review

The first line of evidence that came out that suggested that ephedrine should be the drug of choice for treating hypotension in obstetric anesthesia comes from the many sheep studies that have been carried out in a number of different laboratories. These studies studied chronically instrumented pregnant ewes in which it was possible to measure uterine artery blood flow and fetal and maternal arterial pH. The studies found that when ephedrine was used to maintain or raise blood pressure, uterine blood flow and fetal pH were maintained. Other pressors (e.g. metaraminol or phenylephrine) tended to decrease fetal pH and uterine blood flow.

Evidence from James Eisenach’s lab demonstrated why this was true. In one experiment, they found that:

1. Both ephedrine and metaraminol caused less vasoconstriction of uterine artery samples from pregnant ewes compared to non-pregnant ewes.
2. The exact opposite was true for femoral artery samples. The pressors had a greater effect on the samples from non-pregnant ewes.
3. This means that in pregnant animals, the pressors constricted the femoral artery to a much greater degree compared to the uterine artery. This would tend to enhance uterine blood flow.
4. The difference between the pressors was that the ratio of maximal effect of the drugs in the femoral artery compared to the uterine artery in pregnant animals was 5 for ephedrine and 2 for metaraminol. This means ephedrine will enhance uterine blood flow to an even greater degree than metaraminol.

In another experiment from Eisenach’s lab, they found that nitric oxide synthase (NOS) was up regulated in the uterine artery during pregnancy. The elevated levels of NOS decrease uterine artery responsiveness to pressors that cause vasoconstriction. In addition, they found that ephedrine causes the release of NOS. This causes the uterine artery to constrict even less in the presence of ephedrine compared to other pressors.

In summary, animal and lab data clearly demonstrate that ephedrine preserved uterine artery blood flow and fetal pH to a much better degree than other pressors. From this,
clinicians concluded that ephedrine was the drug of choice to restore blood pressure in pregnant women.

**Umbilical Cord Gas Data**

Unfortunately, when we look at how ephedrine performs when used for restoring blood pressure in pregnant women having spinal anesthesia, the data are disappointing. The most relevant clinical outcome in these studies is the umbilical artery pH. This value tells us how well oxygen was delivered and utilized in the fetus just prior to birth. In no study comparing ephedrine with phenylephrine has the ephedrine group had a higher umbilical pH than the phenylephrine group. In a meta-analysis by Lee et al., they found that on average, the umbilical artery pH was 0.03 higher in the women who received phenylephrine rather than ephedrine.\(^5\) This difference is small, but the data suggest that phenylephrine is the better drug to use in this circumstance.

This pattern is consistent for other pressors as well. In another meta-analysis, Halpern’s group in Toronto found that any pressor or pressor combination out performed pure ephedrine (data presented at the 2002 SOAP meeting but not yet published). Again, no study ever found ephedrine to be the better drug.

More evidence that ephedrine is not a good drug to use in obstetrics comes from studies that use ephedrine to prevent, rather than treat, hypotension. In all these studies, the authors have found that low doses of ephedrine do not effectively prevent hypotension and that higher doses cause significant acidosis in the neonate.\(^6\)\(^-\)\(^8\)

**Metabolic Acidosis**

Some experts feel that umbilical artery pH is not a useful outcome measure. A **respiratory** acidosis in the umbilical cord gas is not predictive of adverse neurological outcomes. However, a **metabolic** acidosis is predictive of adverse neurologic outcomes. In a recent multivariate analysis of a large data set Ngan Kee et al., found an association between ephedrine use and a metabolic acidosis in the umbilical artery.\(^9\) Although the degree of acidosis did not amount to clinically significant levels, this is a worrisome trend in a population of healthy mothers with normal pregnancies having a cesarean deliveries.

**Why Does Ephedrine Cause More Umbilical Artery Acidosis?**

If ephedrine improves blood flow to the to the uterus and increases fetal pH in sheep, why is it associated with greater acidosis in the human fetus? I believe the most likely explanation is that ephedrine increases the metabolic rate in the fetus. A study by Cooper et al. offers evidence that this may be the case.\(^10\) They used an index to assess where the umbilical artery acidosis was occurring. They took the pCO\(_2\) of the umbilical artery and subtracted the pCO\(_2\) of the umbilical vein. They assumed that if this value was large, then the acidosis was being generated in the fetus. What they found was that a low umbilical artery pH was strongly correlated with a high umbilical artery pCO\(_2\) minus umbilical vein pCO\(_2\) in the ephedrine group. They also found that this index was correlated with ephedrine dose. These data are highly suggestive that ephedrine is increasing the metabolic rate of the fetus.

**The Early Fetal Heart Rate Study**

One of the strongest data sets available that ephedrine may be harmful to the fetus comes from Sol Shnider’s group. The paper was published in 1981.\(^11\) They studied laboring women who received epidural analgesia and ephedrine to prevent or treat hypotension. They found that ephedrine increased the fetal heart rate to tachycardic
levels or caused a decrease in variability in over half the patients. Both of these findings were clear signs of fetal distress. Despite this evidence, they assumed that the ephedrine was causing a clinically insignificant change in the fetal heart rate pattern. They assumed that the observed changes were benign because of the wealth of animal data suggesting that ephedrine was the best drug to use in this circumstance.

**Why Are The Laboratory/Animal Data Different Than The Clinical Data?**

Why do the results from these animal studies differ from the clinical studies in humans? Three possible answers to this question:

1. Human vasculature and placental blood flow are different than what is found in sheep.
2. Maybe ephedrine increases the metabolic rate of humans to a greater degree than it does in sheep. Therefore, the beta-agonist stimulation of the metabolic rate seen in humans is not seen in sheep.
3. Maybe the stress of birth unmasked the stress imposed by ephedrine. In the instrumented sheep model, the drugs are given when the animal was not stressed and this might be why the metabolic rate was unaffected. In humans, the ephedrine was given during labor and delivery or during cesarean delivery. The combination of this stress with the ephedrine increased the fetal metabolic rate.

**Clinical Significance**

Some experts will say that these minor differences in cord gases and fetal heart rate strips are not clinically significant and that since blood flow is better preserved with ephedrine, that it should remain the drug of choice. However, it is important to remember that these studies were done on perfectly healthy patients having elective cesarean deliveries or in the case of the fetal heart rate study, vaginal deliveries. These patients and their babies are going to do well even if they get a drug that puts greater stress on the fetus. However, the increased acidosis we see with ephedrine is a sign of a net decrease in the oxygen delivery to the fetus (net delivery being the oxygen delivered minus what is used). It does not matter whether there is increased blood flow with ephedrine, what counts is oxygen delivery and utilization and the net sum of oxygen to the fetus is decreased in the presence of ephedrine. When there is fetal distress or a maternal hemorrhage decreases uterine perfusion, giving a drug that will either decrease oxygen delivery or increase oxygen utilization makes no sense. Better to choose a pressor like phenylephrine to treat the blood pressure.

**Literature Cited**

1. McGrath JM, Chestnut DH, Vincent RD, DeBruyn CS, Atkins BL, Poduska DJ, Chatterjee P: Ephedrine remains the vasopressor of choice for treatment of hypotension during ritodrine infusion and epidural anesthesia. Anesthesiology 1994; 80: 1073-81; discussion 28A


