Dexmedetomidine and Mannitol for Awake Craniotomy in a Pregnant Patient

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We describe the use of dexmedetomidine for an awake neurosurgical procedure in a pregnant patient and quantify the effect of mannitol on intrauterine volume. A 27-year-old woman underwent a craniotomy, with intraprocedural motor and speech mapping, at 20 weeks of gestation. Sedation was maintained with dexmedetomidine. Mannitol at 0.25 g/kg IV was administered to control brain volume during surgery. Internal uterine volume was estimated at 1092 cm³ before surgery and decreased to 770 and 953 cm³ at 9 and 48 hours, respectively, after baseline assessment. No adverse maternal or fetal effects were noted during the intraoperative period or up to 48 hours postoperatively. (Anesth Analg 2015;120:1099–103)

Primary brain tumors rarely present during pregnancy.¹ Awake craniotomy is often indicated for procedures requiring intraoperative monitoring of speech or motor function to facilitate tumor resection while minimizing the risk of compromising neurologic function. Anesthesia options include monitored anesthesia care or general anesthesia with intraoperative awakening. Propofol, used alone or in combination with a short-acting opioid, is commonly used for sedation during awake craniotomy, but patients are at risk for respiratory depression with this technique. Dexmedetomidine is an α2-adrenergic receptor agonist that can be used for sedation during craniotomy requiring intraprocedural speech or motor functional mapping.² The advantages of dexmedetomidine in this setting include titratable sedation and analgesia with minimal respiratory depression.

The management of increased intracranial pressure and volume can be critical to the outcome of neurosurgical procedures. Mannitol produces a reduction in intracranial volume by creating an osmotic gradient across the blood–brain barrier, causing water to leave the brain and enter the intravascular space. To our knowledge, the effect of mannitol use during pregnancy on intrauterine volume and fetal well-being has not been described.³ Complications may arise from induction of a dehydrated maternal state resulting in hypotension and uterine hypoperfusion, potentially leading to fetal injury and fetal dehydration.⁴ Because anesthesia providers may be requested to administer mannitol to patients in the perioperative period, it is critical to understand the impact of this drug on uterine fluid status and fetal well-being. Anesthetic drugs such as dexmedetomidine can potentially affect uterine fluid status, uterine contractility, and fetal well-being, possibly influencing the effect of mannitol on the uterofetal unit.

We describe the use of dexmedetomidine for a craniotomy requiring intraprocedural speech and motor mapping during pregnancy. We also quantify the effect of perioperative mannitol on intrauterine volume and fetal well-being during this procedure.

The patient provided consent to allow the use of her medical information for research and publication.

CASE DESCRIPTION

A 27-year-old gravida 2, para 1 woman at 7 weeks of gestation developed new-onset seizure as well as mild receptive and expressive aphasia. Imaging was deferred until the second trimester of pregnancy, and magnetic resonance imaging without contrast, completed at 16 weeks of gestation, demonstrated a relatively circumscribed intra-axial mass in the posterior superior left temporal lobe measuring 4.5 × 3.2 × 3.5 cm (Fig. 1). The posterior margin of the tumor was adjacent to Wernicke area. She was referred to our institution at 19 weeks of gestation for neurosurgical consultation and was subsequently scheduled for a left frontotemporal craniotomy with intraprocedural motor and speech mapping for resection of the tumor at 20 weeks of gestation.

The patient weighed 70 kg and her height was 172 cm (body mass index 23.8 kg/m²). Given that the effect of mannitol on intrauterine volume or fetal well-being has not been well described, it was decided, in consultation with the patient, that fetal assessment and intrauterine volume assessment would be obtained before surgery and at repeated intervals after surgery and during hospitalization. Informed consent to assess intrauterine volume was obtained from the patient before measurements. The institutional review board deemed this report exempt from research approval because the ultrasonography assessments, including intrauterine volume assessments, were part of the patient’s plan of care. The uterine volume measurements were obtained using abdominal ultrasonography immediately before surgery, in the postanesthesia recovery unit immediately after surgery, on the morning after surgery, and on the second postoperative day by the same individual (BCB).

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Several methods of measuring uterine volume have been described. These include the prolate ellipsoid model, the parallel planimetric area method, and a stepped area-to-volume method. Because uterine volume changes throughout pregnancy, reference volumes also change depending on gestational age. The total intrauterine volume method involves measuring the horizontal and vertical axes of the uterus encompassing the uterine wall, amniotic fluid, and fetus. We report a modification of the total intrauterine volume method, which excluded the measurement of the uterine wall, namely, internal uterine volume. Internal uterine volume is calculated as the product of 0.523 × maximal longitudinal diameter × maximal transverse diameter × maximal anteroposterior diameter of the uterine contents, excluding the myometrium. The purpose of excluding the myometrium is to minimize variations in measurements that may occur as a result of the contractile state of the uterus. The measurement method is illustrated in Figure 2.

Intraoperatively, the patient was monitored with a continuous electrocardiogram, pulse oximeter, noninvasive blood pressure cuff, and skin temperature probe. Two peripheral IV catheters and a radial arterial catheter were inserted. She received supplemental oxygen via a nasal cannula. She was positioned supine with left uterine displacement. Dexmedetomidine was infused initially at 0.4 to 0.5 μg/kg/h without a loading dose. Intermittent boluses of propofol at 10 to 30 mg or fentanyl 25 μg were administered as needed for stimulating events such as urinary catheter placement. Mayfield pinions (Integra LifeSciences Corp., Cincinnati, OH) were placed after infiltration of the pin sites with local anesthetic. A circumferential scalp block was placed using 0.25% bupivacaine with 1:200,000 epinephrine. The dexmedetomidine infusion was decreased to 0.2 μg/kg/h approximately 20 minutes before anticipated motor and speech mapping, and this lower infusion rate was continued during mapping. Speech testing included fluency, naming, and reading. The patient was able to complete these tasks without difficulty. Subsequently, the dexmedetomidine infusion was increased to 0.3 to 0.7 μg/kg/h during tumor resection and surgical site closure. A total of 3400 mL lactated Ringer’s solution was infused IV, total urine output was 800 mL, and estimated intraoperative blood loss was 150 mL. Maternal systolic and diastolic blood pressures remained within 20% of baseline values throughout the procedure with no requirements for pharmacologic manipulation of maternal blood pressure. The total duration of the surgical procedure was 8 hours 29 minutes. The duration of time in the operating room was 9 hours 31 minutes.

Fetal movement and heart tones were assessed intermittently during and after the procedure and were unremarkable. Mannitol was administered as a single dose of 0.25 g/kg IV 3 hours after baseline assessment. Perioperative intrauterine volume measurements are reported in Table 1. Although a change in amniotic fluid volume was apparent by ultrasound, sonographic evidence of oligohydramnios (amniotic fluid index <5 cm or single deepest pocket <2 cm) was not observed.

The procedure and recovery period were uncomplicated. Gross total resection of the brain tumor was confirmed with intraoperative magnetic resonance imaging. Pathological examination revealed an anaplastic (World Health...
Organization grade III oligoastrocytoma. The patient developed no new neurological deficits after the operation and delivered a healthy baby vaginally and uneventfully at term. Because the patient delivered at her home institution, specific details of her labor, delivery, and analgesia used were not available. The mother and child were evaluated 30 months postoperatively; both were in good health with no evidence of tumor recurrence in the mother or medical or developmental concerns in the child.

**DISCUSSION**

**Dexmedetomidine Use During Pregnancy**

Dexmedetomidine is a highly selective, short-acting, $\alpha_2$-adrenergic receptor agonist that can be used to provide sedation, anxiolysis, and analgesia. Propofol, in combination with a short-acting opioid, has traditionally been used for sedation during craniotomy requiring intraoperative patient cooperation; however, there is concern for respiratory depression. Furthermore, hypercarbia may increase the risk for increased intracranial pressure and decreased cerebral perfusion in the neurosurgical patient with reduced intracranial compliance. In contrast to $\gamma$-aminobutyric acid–mimetic drugs and $\mu$-opioid receptor agonists, dexmedetomidine does not cause significant respiratory depression at doses used for sedation. These characteristics make it an ideal sedative drug for craniotomy performed via monitored anesthesia care because access to the airway may be restricted during this procedure.

The effects of dexmedetomidine on the preterm fetus are not well described. It was classified as a US Food and Drug Administration pregnancy category C medication because there are no adequate or well-controlled studies of its use in pregnant women. There are case reports in the literature describing dexmedetomidine use for labor analgesia, for sedation for awake fiberoptic intubation, for sedation for noninvasive ventilation, as an adjunct for cesarean delivery, and as an adjunct for general anesthesia for nonobstetric surgery during pregnancy. Given the limited human research available, we have to rely on animal studies to understand the effects of dexmedetomidine on the pregnant patient and fetus.

Dexmedetomidine has been shown to have a minimal effect on preterm sheep with respect to fetal cardiovascular status and cerebral oxygenation. Dexmedetomidine administration resulted in a decrease in maternal heart rate and blood pressure but no effects on fetal heart rate and mean arterial pressure. Using in utero near-infrared spectroscopy, fetal cerebral oxygenation was measured by assessing changes in oxygenated, deoxygenated, and total hemoglobin. All three measures remained within 5% of baseline during and after dexmedetomidine exposure. Consistent with other case reports, we did not observe fetal bradycardia with dexmedetomidine administration. In rats, chronic in utero exposure to dexmedetomidine resulted in growth retardation and reduced birth weight. However, a single dose of dexmedetomidine resulted in no adverse effects. Dexmedetomidine has also been found to enhance the frequency and amplitude of uterine contractions in both rat and human myometrium in vitro. Although this effect may be advantageous when used for analgesia during labor, this effect is undesirable in preterm, nonobstetric surgical patients. We did not observe any regular uterine contractions during the perioperative period in our patient.

Ala-Kokko et al. using an isolated, perfused term human placenta model, demonstrated that after administration of dexmedetomidine to the maternal perfusate, the ratio of dexmedetomidine in the fetal-to-maternal compartments was $0.77 \pm 0.06$ (mean $\pm$ SD) after 2 hours of perfusion. This value was confirmed by Neumann et al. who measured an umbilical artery-to-maternal venous concentration ratio of 0.76 in a single patient who underwent cesarean delivery after dexmedetomidine administration to facilitate fiberoptic tracheal intubation. Ala-Kokko et al. also measured total content of dexmedetomidine in each compartment; 48.1% $\pm$ 20.3% and 12.5% $\pm$ 5.1% of the total initial amount of dexmedetomidine was located in the placental and fetal compartments, respectively. The placential uptake of dexmedetomidine was significantly higher than that of clonidine (11.3% $\pm$ 3.3%), likely as a result of its higher lipophilicity compared with clonidine. Therefore, the fetal-to-maternal concentration ratio may overestimate total transfer of dexmedetomidine to the fetal compartment if a significant amount of dexmedetomidine remains in the placenta. Our failure to observe intraoperative effects of dexmedetomidine on fetal heart rate and well-being may be the result of the placenta serving as a reservoir, thus limiting fetal exposure to the drug. Further data will be required to confirm this hypothesis.

Unlike other anesthetic drugs with $\gamma$-aminobutyric acid–mimetic or glutamate antagonistic properties, dexmedetomidine does not appear to adversely impact neuronal development. In cultured rodent neocortical neurons, dexmedetomidine did not disrupt axon guidance mechanisms. Also, when administered to neonatal rats, dexmedetomidine did not impair hippocampal synaptic functions. Studies evaluating the effect of dexmedetomidine on brain development in humans are lacking.

**Mannitol and Intrauterine Volume**

Mannitol is used in neurosurgical cases to reduce intracranial edema. However, guidelines for the use and doses of

Table 1. Perioperative Intrauterine Volume Measurements

<table>
<thead>
<tr>
<th>Assessment time point</th>
<th>Time</th>
<th>Uterine measurements (cm)*</th>
<th>Estimated intrauterine volume (cm$^3$)*</th>
<th>Decrease in intrauterine volume from baseline (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>07:30</td>
<td>13.8 × 12.4 × 12.2</td>
<td>1092</td>
<td>—</td>
</tr>
<tr>
<td>Immediately postoperative</td>
<td>19:30</td>
<td>12.5 × 10.9 × 10.8</td>
<td>770</td>
<td>30</td>
</tr>
<tr>
<td>1 day postoperatively</td>
<td>09:45 + 1 day</td>
<td>12.8 × 11.3 × 10.9</td>
<td>825</td>
<td>24</td>
</tr>
<tr>
<td>2 days postoperatively</td>
<td>09:00 + 2 days</td>
<td>13.2 × 11.9 × 11.6</td>
<td>953</td>
<td>13</td>
</tr>
</tbody>
</table>

*Uterine measurements expressed longitudinal diameter × transverse diameter × anteroposterior diameter.

The gestational age was 20 weeks 4 days at baseline. Mannitol (0.25 g/kg) was administered intravenously 3 hours after baseline assessment.
diuretics, particularly of mannitol, during pregnancy are not well established. Christianson and Page reported that the use of diuretics in pregnancy has been associated with early fetal demise, small-for-gestational-age neonates, and preterm labor. However, the diuretics reported by these authors were primarily thiazide diuretics used chronically. In the current case, low-dose (≤0.25 g/kg) mannitol satisfactorily controlled intracranial swelling and did not appear to have adverse effects on the fetus when administered during craniotomy during midgestation pregnancy. However, mannitol resulted in a significant reduction in intrathoracic volume with a subsequent volume recovery during a period of 48 hours. The reduction in internal uterine volume was not associated with any recognized negative sequelae for the fetus.

Significant maternal dehydration can result in dramatic effects on amniotic fluid volume. Traditionally used semi-quantitative techniques such as single deepest pocket or amniotic fluid index provide a rapid snapshot assessment of adequacy of the amniotic fluid volume but have not been used to track acute changes in amniotic fluid volume. In fact, changes in fetal position after successful external cephalic version can result in a significant change in estimated amniotic fluid volumes. Given our interest in serial changes in perioperative uterine and amniotic fluid volume, we explored the use of the total intrauterine volume method. However, an additional concern was that significant changes in the intravascular volume occur with the use of mannitol during neurosurgical procedures, and these changes may increase the probability of uterine contractions. The resulting myometrial thickening during the contraction may falsely skew total intrauterine volume method assessment of the amniotic fluid volume changes. To circumvent these problems, we developed a modified version of uterine volume measurement that limited the measurement to the amniotic fluid, placenta, and fetus only. Presumably, the internal uterine volume measurements are an effective proxy for total fluid change during mannitol treatment given the relative stability in the size of the fetus and placenta over just a few days. Finally, it is important to note that other factors in the perioperative period such as dexmedetomidine or IV-administered fluids may have contributed to the changes in internal uterine volume observed in this patient.

Of note, continuous intraoperative fetal monitoring is not practiced at our institution if the fetus is previable. This need for intraoperative fetal monitoring in this setting is controversial. Although delivery and extraterine survival are not possible, some experts argue that signs of nonreassuring fetal status can be addressed with a number of measures short of delivery. These include confirming adequate maternal oxygenation and blood pressure, modifying maternal position, decreasing the dose or discontinuing the dexmedetomidine infusion, or increasing maternal intravascular volume.

In summary, we describe the use of dexmedetomidine and mannitol during awake craniotomy in a pregnant patient. The dexmedetomidine infusion allowed for titratable sedation and analgesia while facilitating motor and speech mapping for brain tumor resection without notable maternal or fetal adverse effects. Despite its potential benefits, the safety of dexmedetomidine in the obstetric population has not been extensively studied. We also show that the use of a single, low dose of mannitol resulted in a transient 30% reduction in internal uterine volume but had no overt maternal or fetal/neonatal adverse effects either acutely or longitudinally. Further research is required to better understand the effects and safety of both dexmedetomidine and mannitol in the pregnant patient.

DISCLOSURES

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Attestation: Jeffrey J. Pasternak approved the final manuscript and attests to the integrity of the original data and the analysis reported in this manuscript.

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