International Journal of Obstetric Anesthesia 46 (2021) 102974

Contents lists available at ScienceDirect

International Journal of Obstetric Anesthesia

journal homepage: www.elsevier.com/locate/ijoa

Original Article

Association of uterine activity and maternal volatile anesthetic exposure during open fetal surgery for spina bifida: a retrospective analysis

S. Tra [a,*], N. Ochsenbein-Kölble [b,e], P. Stein [c], M. Meuli [d,e], U. Moehrlen [d,e], L. Mazzone [d,e], F. Kraehenmann [b,e], R. Zimmermann [b,e], P. Biro [a,e]

[a] Institute of Anesthesiology, University Hospital Zurich, Zurich, Switzerland
[b] Department of Obstetrics, University Hospital Zurich, Zurich, Switzerland
[c] Institute of Anesthesiology, Emergency Medical Service, Perioperative Medicine, Pain Therapy, Cantonal Hospital Winterthur, Switzerland
[d] Department of Surgery, University Childrens' Hospital Zurich, Zurich, Switzerland
[e] The Zurich Center for Fetal Diagnosis and Therapy, Zurich, Switzerland

ARTICLE INFO

Keywords:
Spina bifida
Fetal surgery
Uterine contractions
Volatile anesthetics

ABSTRACT

Background: Recent warnings postulate a possible damaging effect of volatile anesthetics on the fetus. In our archive of fetal surgeries, we found wide variation in dosing of volatile anesthetics during spina bifida surgeries. We hypothesized that there was an association between volatile anesthetic exposure and uterine activity.
Methods: Sixty anesthesia records from spina bifida operations were assessed. We analyzed the course of the administered volatile anesthetic during surgery and calculated from each patient's anesthesia record the volatile anesthetic exposure expressed in vol%h. We divided the records into two post hoc groups of the 20 lowest exposure (Group L) versus the 20 highest exposure (Group H), and compared them for uterine activity and fetal heart rate.
Results: The number of contractions per hour was significantly greater in Group H (mean 1.3, SD ± 1.2) compared with Group L (mean 0.5, SD ± 0.6, $P = 0.049$). There was no difference between the groups for the administration of the tocolytic drug atosiban ($P = 0.29$). The course of the mean arterial pressure did not significantly differ but group H needed significantly more vasoactive medication ($P < 0.05$).
Conclusions: We found that a lower intra-operative volatile anesthetic exposure than recommended in the MOMS-trial (i.e. <2.0 minimum alveolar concentration [MAC]) was not associated with an increase in intra-operative uterine activity. This is an indication that during spina bifida surgery, 2.0 MAC may not be necessary to avoid potentially harmful uterine activity.

Introduction

The MOMS-trial has produced unequivocal evidence that prenatal spina bifida surgery produces better outcomes than postnatal care.[1,2] Since 2010, in our Zurich Center for Fetal Diagnosis and Therapy (www.swissfetus.ch), more than 135 intra-uterine spina bifida operations have been performed. We have reported crucial aspects, particularly outcomes, complications, and technical advances, from our experiences so far.[3,4] Atosiban (Tractocile®) performs better than magnesium sulphate for tocolysis during spina bifida surgery.[5] Here, we present a retrospective assessment of the association between volatile anesthetic dosing and unwanted intra-operative uterine activity.

During fetal surgery, a primary concern is to avoid uterine contractions, which mainly occur due to uterine manipulation and hysterotomy. Intra-operative uterine contractions can cause serious complications such as bleeding, placental abruption, and umbilical cord compression. Furthermore, they can impede the performance of the operation. Since volatile anesthetics have a suppressive influence on uterine activity, volatile anesthetic dosing plays a crucial role in this context.[6] In the MOMS-trial, it became a standard procedure to administer volatile anesthetic at higher concentrations than required for sufficient maternal sedation. In contrast to anesthesia in non-pregnant women having surgery of comparable invasiveness, it was recommended to administer up to two minimum

* Correspondence to: S. Tra, Institute of Anesthesiology, University Hospital Zurich, CH-8091 Zurich, Switzerland.
E-mail address: sowannara.tra@usz.ch (S. Tra).

https://doi.org/10.1016/j.ijoa.2021.102974
Accepted 19 February 2021

alveolar concentrations (MAC), which for desflurane is >12 vol%.[7] However, in our practice, the mainstay of tocolysis has been atosiban, and the contribution of the volatile anesthetic is considered supplementary.[5]

There is current uncertainty about the relevance of anesthesia-induced neuronal cell death, also referred to as neuro-apoptosis, in the developing brain of human fetuses and infants. Current information is based on studies delivering high doses of anesthetic for long durations in animals. Questions remain regarding both the translation of these findings to humans and the clinical consequences of increased neuro-apoptosis on future neurodevelopment.[8] Nevertheless, reducing the volatile anesthetic concentration in pregnant women is a reasonable endeavour, particularly during long surgical exposures, such as intra-uterine myelomeningocele repair.[9–13] However, volatile anesthetics are tocolytic and thus have a therapeutic role. Unwanted uterine activity may both impair intra-uterine perfusion and precipitate preterm delivery, both of which can adversely impact the fetal brain, so a state of equipoise may exist between high and low volatile anesthetic concentrations.

In our archived records from completed spina bifida surgeries, we noted considerable differences in individual volatile anesthetic dosing between patients, reflecting the different attitudes of attending anesthesiologists. The study aim was to compare the uterine activity, effects on the fetus, intra-operative complications, and variations in the hemodynamic course between patients receiving a high versus low anesthetic exposure.

Methods

The study was approved by the local Ethics Committee (KEK-ZH No. 2015-0172). At admission, each patient gave written consent for the use of her anonymised data, including non-directive prenatal counselling, peri-operative management, maternal-fetal anesthesia and surgery, according to the MOMS-trial (see overview in supplemental Table 1).[2] A fetal surgery program and a web-based data registry were established to collect all pertinent data prospectively and comprehensively.

Retrospective analysis of the patients' records began after 60 operations had been performed. The inclusion criterion was intra-uterine spina bifida repair under tocolytic medication with atosiban used up to 45 h postoperatively according to standard procedures. An initial bolus of 6.75 mg was given immediately before surgery, followed by an infusion of 18 mg/h throughout surgery and 6 mg/h postoperatively.

The data for this study were obtained from three sources:

1. Demographic details from the hospital's general patient records
2. Intra-operative data on uterine contractions and fetal symptoms of distress from the surgeon's report
3. Anesthesia data including the course of volatile anesthetic dosing, maternal hemodynamic parameters, and the choice and dose of vasoactive drugs from the respective anesthetic records.

General anesthesia consisted of induction with thiopental, fentanyl, and rocuronium in a 'rapid sequence' mode, followed by tracheal intubation. Maintenance of anesthesia was with desflurane, continuous neuromuscular block and opioids that penetrate the uteroplacental barrier and additionally provided anesthesia to the fetus. During the intervention, maternal hemodynamics were monitored via an arterial line. Intra-operative fetal heart rate and myocardial contractility was continuously measured using ultrasound and the uterine activity was continuously observed and recorded by a dedicated member of the surgical team. Intra-operative findings such as uterine contraction, placental abruption, and the necessity for fetal resuscitation, were also documented.

To obtain comparability of the entire volatile anesthetic exposure during surgery, we assessed the average end-expiratory concentrations of the volatile anesthetic from each patient's anesthetic record. We calculated the individual total volatile anesthetic exposure, which was the product of the average end-expiratory concentrations of the volatile anesthetic (vol%) and the duration (h) of its application, expressed in 'vol%h'. For this purpose, the entire volatile anesthetic administration period was divided into time segments with constant concentrations. The sum of all these concentration–time products resulted in the final, individual 'total volatile anesthetic exposure'. This parameter best describes the anesthetic burden to which a patient and the fetus have been exposed. Finally, we divided the total volatile anesthetic exposure values of all 60 patients into the two post hoc groups of the 20 lowest (Group L) versus the 20 highest (Group H) exposures. All parameters were compared according to this differentiation.

Data are presented as mean ± standard deviation. A P-value <0.05 was considered significant. Cohen's Kappa was used to measure agreement for categorical items. The Mann-Whitney U test was applied to compare continuous data between the groups and to calculate the P-values. The Mann-Whitney U test was used in a unified way because of its high level of efficacy independent from data distribution. Statistical data were analyzed with IBM SPSS Statistics (version 25, IBM Corporation, Armonk, NY, USA).

Results

The average end-expiratory volatile concentration (vol%) was significantly different between the two groups (P <0.001). This underlines the broad spectrum of dosing regimens used by the anesthesiologists involved. The spectrum of total volatile anesthetic exposure resulted in a broad distribution ranging from the lowest value of 15.4 vol%h to the highest value of 39.9 vol%h. The median total volatile anesthetic exposure was 17.3 vol%h in group L and 28.3 vol%h in group H (P <0.001). An overview of all aspects of desflurane administration is presented in Table 1. The course of the mean arterial pressure did not significantly differ between groups but more treatment with a vasopressor to maintain mean arterial pressure >60 mmHg occurred in group H (Table 1). The two groups did not significantly differ in demographic or pregnancy-related data (Table 2).

The surgery-related data showed no significant difference between the two groups in the operation duration and the duration of the uterus being open, the time for fetal surgery and the length of uterotomy incision (Table 3). There was no evidence that the duration of the operation became shorter over time, so evolution of the operative technique appears unlikely to have influenced the findings.

The main finding was that the number of contractions per hour was significantly higher in Group H (P=0.049). There were no differences between the groups for the standardized administration of atosiban (P=0.29) or for intra-operative fetal bradycardia or postoperative placental abruption within 72 h (Table 4).

Table 1
Clinical data related to anesthesia

	Group L (n=20)	Group H (n=20)	P-value
Total volatile anesthetic exposure (vol% h)	17.3 ± 1.6	28.3 ± 6.1	<0.001
Average expiratory volatile concentration (vol%)	6.6 ± 0.4	10.1 ± 1.3	<0.001
Duration of exposure to volatile agents (min)	158 ± 19	168 ± 28	0.29
Fall in mean arterial pressure from baseline (mmHg)	29.5 ± 9.9	33.1 ± 7.3	0.17
Dose of norepinephrine (μg/min)	4.0 ± 1.3	7.7 ± 4.1	<0.001

Values are presented as mean ± SD.

Table 2
Maternal demographic data.

	Group L (n = 20)	Group H (n = 20)	*P*-value
Height (cm)	167 ± 6	167 ± 5	0.84
Pre-operative BMI (kg/m^2)	27.2 ± 3.7	27.3 ± 4.5	0.99
Postoperative BMI (kg/m^2)	26.7 ± 3.8	26.5 ± 4.5	0.78
Age (y)	32.6 ± 5.5	32.4 ± 4.6	0.93
Week of pregnancy on date of surgery	25.2 ± 0.7	25.2 ± 0.6	0.72
Previous pregnancies (n)	1.1 ± 0.9	1.6 ± 1.6	0.37
Previous cesarean sections (n)	0.3 ± 0.4	0.1 ± 0.3	0.43

Values are presented as mean ± SD. BMI: body mass index.

Table 3
Operation details.

	Group L (n = 20)	Group H (n = 20)	*P*-value
Total operation duration (min)	133 ± 18	148 ± 24	0.06
Duration uterus open (min)	84 ± 14	95 ± 21	0.19
Duration of fetal operation (min)	39 ± 12	46 ± 13	0.08
Length of uterotomy (cm)	7.2 ± 1.1	7.3 ± 1.1	0.72
Necessary intra-operative turns of the fetus (n)	12	7	0.11

Values are presented as mean ± SD or as numbers where appropriate.

Table 4
Intra-operative findings related to the uterus and fetus.

	Group L (n = 20)	Group H (n = 20)	*P*-value
Placental abruption* (n)	0	0	1.0
Fetal bradycardia (n)	4	1	0.43
Fetal resuscitation (n)	0	1	0.80
Total number of contractions (n)	14	33	0.07
Contractions per h (fetal operation)	0.5 ± 0.6	1.3 ± 1.2	0.049
Atosiban (mg)	54 ± 6	57 ± 8	0.29

Values are presented as mean ± SD or as numbers where appropriate (*up to 72 h postoperatively).

Discussion

Globally, an estimated 1800 cases of open fetal surgery have been performed to date. In an animal study Jevtovic-Todorovic et al. reported that anesthetic agents trigger apoptosis in several major brain regions, resulting in deletion of many neurons from the developing brain and residual learning or memory deficits. The increasing concerns about the possible deleterious effects of anesthetics on the fetal brain motivated this investigation. Identifying the optimal volatile concentration during spina bifida surgery remains a challenge.[14]

We interpret our findings in the light of reservations about the exposure of the fetus to anesthetics during spina bifida surgery. In 2009, De Roo et al. found in an animal study that volatile anesthetics can induce a significant increase in dendritic spine density in the somatosensory cortex and the hippocampus.[10] This at least implies that these drugs affect the development of the central nervous system. Davidson et al. reported that volatile anesthetic exposure in the fetal period might cause a delay in neurobehavioral development.[11] In 2011, similar effects were found when the fetus was exposed to propofol, the predominant drug available for the maintenance of intravenous anesthesia.[9] While these investigations only showed a potential impact on neuronal tissue development, more recent studies have indicated that there might be adverse effects on cognitive abilities in the postnatal period.[12,13] Since the latter studies were conducted in animal models, they are of limited relevance for humans. Despite this limitation, the US Food and Drug Administration felt compelled to issue a warning regarding potential impaired brain development in children following exposure to various anesthetic agents (isoflurane, sevoflurane and desflurane) used during mid- and late-pregnancy.[8] These agents represent nearly all the usual volatile maintenance agents, leaving limited options for alternative medications. As a strategic means of minimizing the exposure of the fetus during maternal anesthesia, Otuloye et al. recommended the additional use of gamma-aminobutyric acid agonists, alpha-$_2$ agonists, and opioids (as a means of reducing the dosage of the anesthetics); and secondly to minimize the duration of exposure to anesthetics by limiting the duration of surgery.

We based this investigation on our experience that there are large variations in volatile anesthetic dosing during fetoscopic interventions, independent of the appropriateness of individual doses. This wide range prompted a post-hoc comparison of the association between uterine activity and anesthetic exposure. The main findings were that the frequency of uterine contractions was higher in group H. This suggests that a lower intra-operative anesthetic exposure might not increase the incidence of intra-operative uterine contractions. In addition, a lower volatile anesthetic exposure than recommended initially may not be associated with complications such as bleeding, placental abruption, or umbilical cord compression.

A limitation of this retrospective investigation is that the number of uterine contractions was taken from the surgeon's postoperative report; this seems very subjective. The other limitation is that this study can only show an association between these two factors. It is likely that the anesthetist in charge increased the volatile anesthetic dosing if there were more uterine contractions. In contrast to the MOMS-trial recommendation, delivering volatile anesthetic concentrations below 2.0 MAC (e.g. 1.0 MAC) might be acceptable, provided this is adapted to the mother's hypnotic needs.

The less pronounced hemodynamic effects associated with reduced dosing of volatile anesthetic and the need for fewer interventions with vasoconstrictors to maintain stable maternal hemodynamics and uterine perfusion may be additional benefits of avoiding a high-dose regimen.

Boat et al. proposed adding a continuous infusion of propofol while administering a lower volatile anesthetic regimen.[15] It is unclear whether this mixed-method approach maintains better hemodynamic stability and uterine perfusion. We do not know whether atosiban was sufficient alone to dampen uterine activity during uterotomy, or to what extent volatile anesthetic contributed.

In conclusion, in this retrospective study the administration of a lower intra-operative volatile anesthetic dose and reduced exposure did not appear to increase the risk of uterine contractions. If these findings are confirmed, it would be reasonable to administer volatile anesthetic concentrations according to the maternal anesthetic requirements, thus reducing the total exposure of the fetal brain.

Declaration interests

PB is a medical adviser of Guide In Medical, Nazareth, Israel, and has received travel allowances from Merck Sharp & Dohme AG, Switzerland. All other authors have no conflicts to declare.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijoa.2021.102974.

References

1. Adzick NS, Sutton LN, Crombleholme TM, Flake AW. Successful fetal surgery for spina bifida. *Lancet*. 1998;352:1675–1676.
2. Adzick NS, Thom EA, Spong CY, et al. A randomized trial of prenatal versus postnatal repair of myelomeningocele. *New Engl J Med*. 2011;364:993–1004.
3. Kahr M, Winder F, Vonzun L, et al. Open intrauterine fetal myelomeningocele repair: Changes in the surgical procedure and perinatal complications during the first 8 years of experience at a single center. *Fetal Diagn Ther*. 2020;47:485–490.
4. Mazzone L, Moehrlen U, Casanova B, et al. Open spina bifida: Why not fetal surgery? *Fetal Diagn Ther*. 2019;45:430–434.
5. Ochsenbein-Kölble N, Krähenmann F, Hüsler M, et al. Tocolysis for in utero surgery: atosiban performs distinctly better than magnesium sulfate. *Fetal Diagn Ther*. 2018;44:59–64.
6. Yoo KY, Lee JC, Yoon MH, et al. The effects of volatile anesthetics on spontaneous contractility of isolated human pregnant uterine muscle: a comparison among sevoflurane, desflurane, isoflurane, and halothane. *Anesth Analg*. 2006;103:443–447.
7. Ferschl M, Ball R, Lee H, Rollins MD. Anesthesia for in utero repair of myelomeningocele. *Anesthesiology*. 2013;118:1211–1223.
8. Olutoye OA, Baker BW, Belfort MA, Olutoye OO. Food and Drug Administration warning on anesthesia and brain development: implications for obstetric and fetal surgery. *Am J Obstet Gynecol*. 2018;218:98–102.
9. Briner A, Nikonenko I, De Roo M, Dayer A, Muller D, Vutskits L. Developmental stage-dependent persistent impact of propofol anesthesia on dendritic spines in the rat medial prefrontal cortex. *Anesthesiology*. 2011;115:282–293.
10. De Roo M, Klauser P, Briner A, et al. Anesthetics rapidly promote synaptogenesis during a critical period of brain development. *PLoS ONE*. 2009;4:e7043.
11. Davidson AJ. Anesthesia and neurotoxicity to the developing brain: the clinical relevance. *Paediatr Anaesth*. 2011;21:716–721.
12. Hansen TG, Engelhardt T. Long-term neurocognitive outcomes following surgery and anaesthesia in early life. *Curr Opin Anaesthesiol*. 2018;31:297–301.
13. Baud O, Saint-Faust M. Neuroinflammation in the developing brain: risk factors, involvement of microglial cells, and implication for early anesthesia. *Anesth Analg*. 2019;128:718–725.
14. Jevtovic-Todorovic V, Hartman RE, Izumi Y, et al. Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. *J Neurosci*. 2003;23:876–882.
15. Boat A, Mahmoud M, Michelfelder EC, et al. Supplementing desflurane with intravenous anesthesia reduces fetal cardiac dysfunction during open fetal surgery. *Paediatr Anaesth*. 2010;20:748–756.