Title

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Journal

Fetal Diagnosis and Therapy, 47(11)

ISSN

1015-3837

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Publication Date

2020

DOI

10.1159/000509384

Peer reviewed

HHS Public Access

Author manuscript

Fetal Diagn Ther. Author manuscript; available in PMC 2022 August 11.

Published in final edited form as:

Fetal Diagn Ther. 2020 ; 47(11): 810–816. doi:10.1159/000509384.

Use of Remifentanil for Open *In Utero* Fetal Myelomeningocele Repair is Associated with a Reduction in the Volatile Anesthetic Concentration Required to Maintain Uterine Relaxation

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Abstract

Open fetal repair of myelomeningocele (MMC) is an option for prenatally diagnosed spina bifida. Historically, high dose volatile anesthetic was used for uterine relaxation, but is associated with fetal cardiovascular depression. We examined the impact of administering a supplemental remifentanil infusion on the concentration of inhaled anesthetic required for intraoperative uterine relaxation.

We retrospectively analyzed 22 consecutive patients who underwent open fetal MMC repair with desflurane anesthesia from 2014–2018. The anesthetic protocol was modified to include high dose opioid with remifentanil in 2016. We examined intraoperative end-tidal desflurane concentrations, vasopressor use, incidence of umbilical artery Doppler abnormalities, and incidence of preterm labor and delivery.

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Author Contributions:

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JS: This author contributed to literature review, data analysis, and editing of the manuscript.

ELW: This author contributed to the data analysis, statistical analysis and editing of the manuscript.

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Statement of Ethics: Study protocol was approved by the Institutional Review Board. Written informed consent was not obtained because this was a retrospective study.

Disclosure Statement: None Declared

Patients (n=11) who received desflurane and remifentanil (Des/Remi) were compared to patients (n=11) who received desflurane (Des) alone. Intraoperatively, the maximum end-tidal desflurane required to maintain uterine relaxation was lower in the Des/Remi group (7.9% ± 2.2% vs. 13.1% ± 1.2%, p<0.001). The mean phenylephrine infusion rate was also lower in the Des/Remi group (36 ± 14 vs. 53 ± 10 mcg/min, p=0.004).

Use of opioid with supplemental remifentanil was associated with lower volatile anesthetic dosing and decreased vasopressor use; fetal outcomes were not different. Remifentanil may allow decreased volatile anesthetic while maintaining adequate uterine relaxation.

Keywords

fetal anesthesia; fetal surgery; myelomeningocele; umbilical artery flow; uterine relaxation

Introduction:

Myelomeningocele (MMC) is a neural tube defect affecting 5–10 pregnancies per 10,000 in the United States. (1) Compared to postnatal closure, open fetal surgery between 19–26 weeks gestation for MMC repair improves postnatal outcomes. (2) Accordingly, the number of centers performing open MMC repair has increased (3, 4), and new anesthetic techniques are being examined. (5)

Maintaining maternal and fetal stability during open repair while facilitating surgical exposure presents unique challenges for the anesthesiologist. Profound uterine relaxation is required for appropriate surgical conditions and adequate uterine perfusion. (6) Historically during the MOMs trial, high maternal doses of inhaled anesthetic agents [>2 minimum alveolar concentration (MAC)] were used for uterine relaxation, and intraoperative opioids were minimized in an effort to allow easier maintenance of maternal blood pressure. (2) However, use of high dose vapor is associated with fetal cardiovascular depression (6–9), and may also cause abnormal umbilical artery flow. (10) In the United States, anesthesia for open fetal surgery was no longer standardized following the MOMS trial. (2)

Adding supplemental infusions of propofol and remifentanil to a volatile anesthetic-based technique improves intraoperative fetal stability. (5) In an animal model, this technique is associated with improved hemodynamics, uterine blood flow, and fetal acid-base status compared to high dose volatile anesthetic alone. (11) However, it is not clear if both propofol and remifentanil are necessary to achieve the desired reduction in volatile anesthetic concentration required for maintaining uterine relaxation. Propofol decreases human uterine muscle contractility *in vitro* (12, 13), but due to its high plasma protein binding (>95%), plasma free propofol concentration is too low to affect uterine tone at clinically relevant dose ranges. (13) Propofol is also a myocardial depressant and may have negative effects on both mother and fetus. Opioid receptors have been identified on human myometrium and, when activated, lead to relaxation *in vitro* (14), suggesting a potential benefit of increasing intraoperative opioid administration.

As a site member of the MOMS trial, we initially used and continued to use a high-dose volatile anesthetic-based technique with minimal opioid administration until 2016. (2) With increasing evidence that a high-dose volatile technique might negatively impact the fetus (5), we changed our practice from a primarily high-dose volatile anesthetic to one that was supplemented with significant intraoperative opioid administration. Following the practice change, fentanyl was administered at induction with the initiation of a remifentanil maintenance infusion to potentially decrease inhaled anesthetic requirement.

In this before-after study, our primary aim was to determine the impact of supplemental opioid on the desflurane concentration required for adequate intraoperative uterine relaxation. Additionally, we compared the effects of this technique on maternal hemodynamics and fetal parameters during open fetal surgery.

Methods:

Study population

After IRB approval, we performed a retrospective review of all 24 patients who underwent open fetal MMC repair between 2014–2018 at a US tertiary care medical center, with the open fetal surgery anesthetic protocol change occurring in early 2016. All surgeries included in the study were performed by one primary surgeon, whose surgical approach remained consistent over the study period, and who had been in practice as a fetal surgeon since the start of the MOMS trial. Two patients who received sevoflurane instead of desflurane were excluded from the analysis, leaving 22 patients for consideration. We followed the STROBE guidelines in completing this study. (15)

Maternal-fetal anesthetic management

All patients scheduled for open fetal MMC repair underwent routine preoperative assessment by a multidisciplinary team. A thorough in-person preoperative history and physical was performed by an anesthesiologist within 2 weeks prior to the surgery date and again on the day of surgery. Before induction of maternal general anesthesia, a lumbar epidural was placed for postoperative pain management. All patients underwent general endotracheal anesthesia with a rapid sequence induction. For anesthesia maintenance, all patients received high-dose desflurane without a remifentanil infusion prior to 2016, as previously detailed. Although intravenous fentanyl administration was not standardized, total doses remained ≤ 100mcg for all of these patients, with the majority of patients not receiving any fentanyl until after uterine closure. In 2016, the anesthetic protocol was altered, with the administration of 250 mcg of intravenous fentanyl on induction, immediately followed by initiation of an intravenous infusion of remifentanil at 0.3 mcg/kg/min which remained constant throughout the case until emergence. Inhaled desflurane was administered to achieve adequate uterine relaxation. Prior to 2016, our institutional protocol was to increase desflurane to near 2 MAC just prior to uterine exposure and titrate the vapor concentration up or down based on the surgeon's evaluation of the uterus. After the protocol change in 2016, where patients were administered a remifentanil infusion, the desflurane was typically increased to 1–1.5 MAC just prior to uterine exposure, and the concentration titrated up or down based on surgical feedback of uterine tone. All

patients received a phenylephrine infusion to maintain their mean arterial pressure within 10% of baseline as well as glycopyrrolate or ephedrine boluses to maintain maternal heart rate near baseline (typically within 20%). This hemodynamic protocol is similar to the recent guidelines for the management of maternal hemodynamics during cesarean delivery. (16) Intermittent fetal echocardiography and umbilical artery Doppler ultrasound were used for fetal monitoring. For fetal anesthesia, intramuscular fentanyl and rocuronium were administered to the fetus in all cases following maternal hysterotomy. Additional uterine tocolysis included preoperative indomethacin and administration of intravenous magnesium sulfate (6 gram load over 20 minutes, followed by an infusion of 2 grams per hour) at start of uterine closure. Following the completion of uterine closure and magnesium load, the desflurane concentration was gradually reduced during abdominal closure in preparation for emergence. During this time, the epidural analgesia was initiated.

Medical records were reviewed to determine intraoperative end-tidal desflurane concentrations, vasopressor use, incidence of umbilical artery flow abnormalities, presence of intraoperative uterine contractions, and incidence of preterm labor and delivery. MAC was determined by dividing end-tidal % desflurane by 6.6%. (17)

Statistical analysis

Data are reported as mean ± standard deviation or median [interquartile range] for continuous variables, depending on normality, and as count (percentage) for categorical variables. This study was designed as a retrospective superiority trial with the prespecified primary outcome as maximum end-tidal percentage of desflurane between procedure start (i.e., surgical incision) and procedure end (i.e., surgical closure), compared between patients who received a remifentanil infusion versus those who did not. Maximum end-tidal concentration of desflurane was chosen as an endpoint to demonstrate the degree of volatile anesthetic required to maintain adequate uterine relaxation, similar to a prior study evaluating the effect of supplemental propofol and remifentanil. (5) After confirming that the maximum end-tidal desflurane dose was normally distributed, the primary analysis used a Student’s t-test.

Secondary outcome univariate analyses were performed with t-tests or Mann-Whitney U tests for continuous variables, depending on normality, and Fisher’s Exact Test for all categorical variables given the small sample size. Data are displayed as mean ±SD, median (interquartile range) or number (percent).

Since operative duration was statistically shorter after the anesthetic practice change, we performed a post-hoc sensitivity analysis adjusting the reported measurements of total volatile anesthetic concentration by operative time using linear regression. Recognizing the limitations of the small sample size, no other adjustment factors were used. All analyses were performed using Stata MP ver. 14 (StataCorp LP).

Sample Size Calculation

The sample size calculation was based on a primary outcome of maximum end-tidal desflurane percentage. Analysis of fetal anesthesia data prior to 2016 demonstrated an average maximum desflurane concentration of 13% with a standard deviation (σ) of

about 1.3%. Although reflective of our recent practice, a standard deviation of 1.3% was unexpectedly small, and we felt it was a potentially unrealistic assumption that the data incorporating the supplemental opioid would remain with a standard deviation near this value. Consequently, we chose to use data from the 2010 article by Boat et al. (5) In this work, the volatile-based fetal anesthesia group received a mean maximum desflurane dose of 15.8 ± 3.0% and the group that received intravenous propofol and remifentanil had a mean maximum desflurane concentration of 10.6 ± 4.3%. This represents a 40% dose reduction in maximum desflurane concentration, which is the difference we chose to use for our sample size calculation. Using the mean value from our prior data (Group 1) combined with the unequal σ's from Boat et al. (5), a two group Satterthwaite t-test with a 0.05 two-sided significance level will have 88.45% power to detect a difference in means of 5.2% (the difference between a Group 1 mean, μ_1, of 13% and a Group 2 mean, μ_2, of 7.8%, which represents a 40% reduction) assuming that the Group 1 standard deviation, σ_1, is 4.3% and the Group 2 standard deviation, σ_2, is 3.0% (ratio of Group 2 to Group 1 standard deviation is 0.698) when the sample sizes in the two groups are 11 and 11, respectively.

Results:

Eleven consecutive patients who received desflurane and supplemental opioid (Des/Remi) were compared to the 11 previous patients (control) who received desflurane (Des) without remifentanil or significant fentanyl administration prior to uterine closure. Maternal age, weight, and gestational age did not significantly differ between the groups (Table 1). Two patients had depression, and 1 had asthma in the Des/Remi group. One patient had depression, 1 had asthma, and 1 had hypothyroidism in the Des group. Preoperative baseline maternal HR and MAP did not significantly differ between groups. The upper border of the fetal MMC lesion in both groups ranged from L1-S1. Preoperative fetal echocardiography was normal in both groups except for 1 patient in the Des/Remi group notable for a small ventricular septal defect. The average gestational age at surgery was similar, 24.0 ± 1.3 weeks in the Des group vs. 24.3 ± 1.2 weeks in the Des/Remi group (Table 1).

Intraoperative findings are displayed in Table 2. The maximum end-tidal desflurane required from procedure start to procedure end was lower in the Des/Remi group (7.9 ± 2.2% vs. 13.1 ± 1.2%, $p<0.001$). The duration of surgery was 17% longer in the Des group than the Des/Remi group (2.7 ± 0.3 vs. 2.3 ± 0.3 hours, $p=0.005$).

In addition, the Des/Remi group was administered less total desflurane than patients maintained on desflurane alone (Des group). After adjustment for procedure length, use of supplemental remifentanil was associated with a mean 1.3 MAC*hour [95% CI 0.5 to 2.0, $p<0.001$] reduction in total desflurane use between incision and closure (Table 2). As expected, following the protocol change, total fentanyl prior to uterine closure (250 [250 – 250] mcg vs. 0 [0 – 0] mcg, $p<0.001$) and case-average remifentanil (0.3 [0.2 – 0.4] vs 0 [0–0] mcg/kg/min, $p<0.001$) administration was higher in the Des/Remi group.

The average phenylephrine infusion rate was lower in the Des/Remi group (36 ± 14 vs. 53 ± 10 mcg/min, $p=0.004$). Maximum maternal heart rate and maximum and minimum maternal mean arterial pressure did not differ significantly between groups; minimum heart rate was

significantly lower in the Des/Remi group, and median glycopyrrolate dose was higher. The average amount of intravenous crystalloid and colloid in each group was not different. One patient in each group received an intraoperative maternal blood transfusion.

Regarding intraoperative fetal hemodynamics, there was no difference in reversal or absence of umbilical artery end diastolic flow in either group, and there were no observed occurrences of fetal bradycardia (Table 2). Significant fetal cardiac dysfunction requiring administration of fetal resuscitation medications or altering the surgical conduct of the MMC repair was not noted in either group with intermittent intraoperative echocardiography.

Adequate uterine relaxation was achieved and maintained in both groups. No intraoperative uterine contractions were observed in either group. Estimated median intraoperative blood loss was 300 ml in the Des group vs. 100 ml in the Des/Remi group (p=0.02).

Additionally, there was no difference in the incidence of preterm labor or delivery between the two groups, and the average birth weight was similar between the two groups (2250 ± 584 vs. 2515 ± 430 grams, p=0.28). Postoperative fetal echocardiography was unchanged in all patients (Table 3).

Discussion:

Anesthesia for open fetal surgery is an area that continues to evolve. Though historically the anesthetic practice for open fetal surgery used high-dose volatile anesthetics alone to maintain uterine relaxation, our results demonstrate that supplemental opioid utilizing a remifentanil infusion is associated with a reduction in the concentration of anesthetic vapor dose required to maintain adequate uterine relaxation and appears to be a reliable and safe anesthetic technique. The 40% reduction in required end-tidal desflurane concentration we observed is similar to that observed in a prior study by Boat et al. that administered infusions of both remifentanil and propofol in the group requiring less volatile anesthetic. (5)

In an effort to reduce the inhaled anesthetic agent required to maintain intraoperative uterine relaxation, we examined the addition of significant supplemental opioid using a remifentanil infusion, without the use of supplemental propofol. The reduced volatile anesthetic concentration associated with the use of supplemental opioid allows its effects on maternal hemodynamics and fetal myocardial depression to be minimized. (18) In addition, there may be a benefit to decreasing the exposure of the developing fetal brain to potentially neurotoxic agents contained in both volatile anesthetics and propofol. (19) In 2016, the United States Food and Drug Administration issued a warning that repeated or lengthy use of general anesthesia in children younger than 3 years or in pregnant women during their third trimester may affect the development of children’s brains. (19) Though it is not clear if this warning should extend into the second trimester (when most open fetal procedures are performed), minimizing exposure is likely preferable. Additionally, it is possible that the degree of neurotoxicity is dose-dependent (20, 21), so strategies to reduce total exposure by using supplemental opioid infusion of remifentanil may be beneficial as opioids are considered non-neurotoxic.

Previous work from our institution demonstrated an increased incidence of umbilical artery flow abnormalities with the use of sevoflurane when compared to desflurane. Although all volatile anesthetics are myocardial depressants, desflurane may have improved cardiac output and heart rate compared to sevoflurane. (22) Consequently, we elected to preferentially use desflurane for all open fetal cases unless contraindicated. Unlike other published supplemental anesthesia protocols for open fetal surgery (2, 5), we decided to avoid propofol for our cases, as there is no evidence to support the use of propofol for uterine relaxation at typical anesthetic levels. (13) In addition, propofol is a known myocardial depressant that may contribute to unfavorable fetal hemodynamics, and propofol may be neurotoxic to the developing brain.

In our study, we also noted a statistically significant reduction in average phenylephrine rate in the patients who received remifentanil and desflurane when compared to those who received desflurane alone (36 ± 14 vs. 53 ± 10 mcg/min, p=0.004). A more stable maternal hemodynamic state that requires less vasopressor associated with the use of supplemental remifentanil and decreased desflurane concentration may offer improved fetal perfusion and well-being during these complex procedures.

The use of supplemental remifentanil for open fetal surgery offers several advantages in clinical practice. Remifentanil readily crosses the placenta, providing fetal analgesia and reducing fetal sympathetic response to surgery. (23, 24) It is also rapidly metabolized in both the mother and the fetus, and remifentanil pharmacokinetics in mid-gestation during fetal surgery have been shown to be similar to the general population. (25) One drawback of remifentanil is the potential development of opioid-induced hyperalgesia, which can lead to higher postoperative pain scores and delayed recovery after surgery. (26) Similar to patients in the MOMS trial, lumbar epidural catheters continue to be placed for all patients undergoing open fetal repair at our institution to provide opioid-sparing analgesia and reduce the potential for poorly controlled postoperative pain increasing the risk of uterine contractions. (2) Bradycardia is another reported side effect of remifentanil. (27) Intraoperative minimum maternal heart rate was 10 bpm lower in the patients who received remifentanil, and median total intraoperative glycopyrrolate dose was 0.2mg higher; however, we observed no significant fetal bradycardia in any of these cases. This is supported by trials examining the use of remifentanil for labor analgesia. Although data are limited, when compared to neuraxial analgesia, there is no evidence of decreased Apgar scores, concerning cord gases, or increased need for neonatal resuscitation despite using remifentanil through the second stage of labor. (28–30)

The before/after nature of this study has some limitations. First, the procedure length was 17% longer in the Des group than the Des/Remi group (2.7 ± 0.3 vs. 2.3 ± 0.3 hours, p=.005). It is unclear what the cause of this result is from as a single surgeon performed all cases in the time period and had been performing these procedures for over 10 years. However, the difference in desflurane dosing was not simply due to procedure length, as it persisted after adjustment for procedure duration. Second, the practice change included a 250mcg bolus of fentanyl at anesthesia induction as part of the opioid supplementation of the anesthetic. However, it is unlikely that fentanyl bolus dose at anesthetic induction contributes significantly to the favorable results in the Des/Remi group, as the median

duration between induction and uterine incision (53 minutes) implies that over 90% of fentanyl would have already been eliminated from the plasma before uterine incision. (31) Due to the retrospective design of our study, there is also the potential for time-dependent confounding and the continuation of a pre-intervention trend that could lead to bias. Another potential source of bias is the Hawthorne effect, where providers in the Des/Remi group may have unintentionally modified other aspects of their clinical management following the protocol change. Our retrospective, before and after study design limits our conclusions to be interpreted as an association with the use of remifentanil and decreased dose of volatile anesthesia rather than a certainty of cause and effect.to allow for optimal surgical conditions in these cases.

A further limitation is the small sample size. Due to the relatively rare occurrence of congenital anomalies amenable to fetal intervention, randomized controlled trials are difficult to perform at a single institution. (18) Future work we hope to pursue includes a prospective, multicenter trial validating this anesthetic technique. In addition, further studies are needed to examine the effects of remifentanil on uterine tone and fetal cardiac function. Additionally, as more prenatal MMC repairs are being performed fetoscopically, our technique should be validated in this patient group.

In summary, we demonstrate the feasibility of an anesthetic protocol for MMC repair, which uses opioid supplementation with a remifentanil infusion that is associated with reduced desflurane administration and yields similar intraoperative and postoperative maternal and fetal outcomes. We propose that remifentanil offers a viable alternative to high-dose volatile anesthetic use in these procedures and also obviates the need for supplemental propofol.

Acknowledgements:

We gratefully acknowledge the Fetal Treatment Center at the University of California San Francisco.

Funding Sources:

Support was provided from institutional and/or departmental sources. ELW was supported by NIH KL2TR001870

Glossary of Terms

HR	Heart rate
MAP	Mean arterial pressure
MMC	Myelomeningocele
MOMS	Management of Myelomeningocele Study
MAC	Minimum Alveolar Concentration
Des	Desflurane
Des/Remi	Desflurane and remifentanil

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Table 1.

Preoperative Data of Patients Receiving Desflurane Alone (Des) vs. Desflurane and Remifentanil (Des/Remi)

	Des	Des/Remi	p value
Total Number of Patients	11	11	
Demographics			
Year of surgery			
2014–15	11	0	
2016–18	0	11	
Maternal age (years)	31.0 ± 5.4	30.7 ± 4.5	0.90
Maternal weight (kg)	78.8 ± 11.6	74.2 ± 9.6	0.32
Gestational age at surgery (weeks)	24.0 ± 1.3	24.3 ± 1.2	0.55
Preoperative maternal heart rate (beats/min)	84 ± 16	79 ± 13	0.42

MAC = minimum alveolar concentration (i.e., end-tidal desflurane percentage divided by 6.6%)

* Categorical variables were compared with Fishers' Exact Test due to small sample size

Continuous data are displayed as mean ±SD

Table 2.

Intraoperative Data of Patients Receiving Des vs. Des/Remi

	Des	Des/Remi	p value
Intraoperative Variables			
Duration of anesthesia (hours)	3.28 ± 0.22	3.00 ± 0.37	0.049
Duration of surgery (hours)	2.69 ± 0.26	2.30 ± 0.31	0.005
Maximum maternal heart rate (beats/min)	122 [116–138]	122 [112–129]	0.49
Minimum maternal heart rate (beats/min)	62 [58–72]	52 [50–54]	0.005
Maximum maternal MAP	109 [103–118]	103 [100–119]	0.17
Minimum maternal MAP	67 [63–69]	63 [58–65]	0.075
Case-average end-tidal desflurane	11.0 ± 1.2%	6.7 ± 2.1%	<0.001
Maximum end-tidal desflurane	13.1 ± 1.2%	7.9 ± 2.2%	<0.001
Total MAC-hour desflurane exposure **	4.5 ± 0.7	2.4 ± 1.0	<0.001
Case-average phenylephrine rate (mcg/min)	53 ± 10	36 ± 14	0.004
Total fentanyl dose prior to uterine closure (mcg)	0 [0–0]	250 [250–250]	<0.001
Case-average remifentanil dose (mcg/kg/min) #	0 [0–0]	0.3 [0.2–0.4]	<0.001
Total glycopyrrolate dose (mg)	0.4 [0–0.6]	0.6 [0.4–0.8]	0.025
Estimated blood loss (mL)	300 [100–300]	100 [50–150]	0.022
Colloid volume (L)	0.5 [0.5–1.0]	0.5 [0–1.0]	0.60
Crystalloid volume (L)	1.3 ± 0.5	1.0 ± 0.6	0.26
Reversal of umbilical artery end diastolic flow	3 (27%)	2 (18%)	>0.99 *
Incidence of fetal bradycardia	0	0	>0.99

Data are displayed as mean ±SD, median [interquartile range] or number (percent).

* Categorical variables were compared with Fishers' Exact Test due to small sample size

** Exposure time from procedure start to procedure end

Table 3.

Postoperative Data of Patients Receiving Des vs. Des/Remi

	Des	Des/Remi	p value
Postoperative Outcomes			
Postop contractions on POD #0	1 (9%)	0	>0.99 *
Contractions on POD #1–3	3 (27%)	3 (27%)	>0.99 *
Preterm labor	3 (27%)	4 (36%)	>0.99 *
Median gestational age at birth (weeks)	36 [31–36]	35 [33–36]	0.54
Birth weight ** **(g)**	2250 ± 584	2515 ± 430	0.28

POD = postoperative day

Data are displayed as mean ±SD, median (interquartile range) or number (percent)

* Categorical variables were compared with Fishers' Exact Test due to small sample size

** Missing 3 values