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Tocolysis for in utero Surgery: Atosiban Performs Distinctly Better than Magnesium Sulfate

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Abstract
Introduction: To compare tocolysis with magnesium sulfate versus atosiban regarding the occurrence of short-term preterm labor and maternal side effects during and after open fetal myelomeningocele (MMC) repair. ***Material and Methods:*** A prospective nonrandomized cohort study was performed including 30 fetal MMC cases. The first 15 cases (group 1) received magnesium sulfate according to the MOMS protocol. In the following 15 cases (group 2), magnesium sulfate was substituted by atosiban. Chorioamniotic membrane separation (CMS), premature prelabor rupture of the fetal membranes (PPROM), preterm delivery <3 weeks after fetal MMC repair, and maternal complications due to the tocolytic medication were the major endpoints. ***Results:*** In both groups, one CMS but no PPROM was diagnosed <3 weeks after fetal MMC repair. One patient of group 2 delivered <3 weeks after fetal MMC repair because of an intraoperative placental abruption at 25 weeks. All women of group 1 showed an electrolyte imbalance during magnesium sulfate administration. One woman of group 1 developed several episodes of a third-degree atrioventricular block within the first 3 days after fetal surgery. Lethargy was found in all women during magnesium sulfate therapy. No maternal side effects were found under atosiban. ***Discussion:*** The use of atosiban resulted in an almost identical short-term uterine outcome without any serious maternal complications as seen when magnesium sulfate was given. Thus, the authors suggest using atosiban instead of magnesium sulfate in the context of open fetal surgery.

Introduction

Open fetal myelomeningocele (MMC) repair is an innovative therapeutic option in selected cases [1] since the results of the MOMS trial showed that prenatal repair produces better outcomes than postnatal repair [2]. However, one of the main concerns after open fetal surgery is

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potentially deleterious preterm labor. Beside cervical dilatation, increased uterine contractility and rupture of the chorioamniotic membranes are factors inducing preterm labor [3, 4]. To minimize the risk of an increased uterine contractility after open fetal MMC repair, tocolytics are applied. The tocolytics used in the MOMS trial were high doses of magnesium sulfate and indomethacin perioperatively followed by nifedipine.

The aim of this paper was to compare two different tocolytic regimens, namely magnesium sulfate and atosiban, with regard to short-term preterm labor and maternal side effects. Chorioamniotic membrane separation (CMS), premature prelabor rupture of the fetal membranes (PPROM), and preterm deliveries <3 weeks after fetal MMC repair as well as maternal complications due to the tocolytic medication were the major endpoints.

Material and Methods

From December 2010 till December 2015, a total of 30 fetal MMC repair operations were performed at the Zurich Center for Fetal Diagnosis and Therapy (www.swissfetus.ch). In this prospective nonrandomized cohort study, all patient data were entered in our fetal MMC repair database. The usual maternal and fetal stem data as well as maternal and fetal outcomes were documented in detail. The study was conducted in accordance with the approval of the ethics commission Zurich (KEK-ZH No. 2015-0172).

Inclusion criteria for maternal-fetal surgery were singleton pregnancy, MMC with the upper level located between T1 and S1, evidence of hindbrain herniation, gestational age (GA) of 19–25.9 weeks, normal karyotype, maternal age of at least 18 years, and maternal BMI <40. Major exclusion criteria were additional fetal malformations unrelated to MMC, severe kyphosis >30°, short cervix or previous preterm birth, placenta previa, former placental abruption, maternal HIV or hepatitis B/C positivity, uterine abnormality (big or multiple fibroids), previous hysterotomy in the active uterine segment, psychosocial problems, and any other contraindication for major surgery. Women with a fetal MMC referred to our center were evaluated in a standardized way by sonography and a fetal MRI prior to comprehensive prenatal counseling. If the patient qualified for fetal MMC repair, written informed consent was obtained, and the fetal operation was scheduled to occur between 22–26 gestational weeks (GW). The fetal MMC repair was performed by fetal surgeons according to standardized operative techniques as reported in the MOMS trial. Fetal monitoring (fetal heart rate and myocardial contractility) was ascertained by continuous sterile ultrasound throughout the operation. Uterine relaxation was monitored clinically during the entire intervention. Postoperatively, contractions were monitored clinically as well as via cardiotocography (CTG) in a standardized fashion.

Perioperative tocolysis was performed with two different regimens, one based on magnesium sulfate (group 1), the other based on atosiban (group 2). These two groups were then compared.

Group 1

The first 15 cases (cases 1–15) were managed by a modified MOMS trial protocol during the first 36 h: they received 100–200 mg indomethacin perioperatively, 6 g of magnesium sulfate at the time of the hysterotomy closure as an intravenous bolus over 20 min followed by a continuous magnesium sulfate infusion of 4 g/h for 2 h and 3 g/h thereafter for 6 h. If there was no evidence of significant uterine irritability or contractions, the magnesium sulfate dose was gradually decreased to 2–2.5 g/h with a target plasmatic magnesium level of 3.0–3.3 mmol/L (=7.3–8 mg/dL). After the first 24 h, magnesium sulfate was stopped and the patient received oral nifedipine 120 mg/day till delivery. In deviation from the MOMS protocol, atosiban, a selective oxytocin receptor antagonist, or hexoprenaline, a betamimetic agent, served as emergency medication to abolish contractions (both substances not approved by the Food and Drug Administration [FDA] in the US). One cycle of atosiban included a 6.75-mg i.v. bolus followed by 18 mg/h over 3 h and 6 mg/h for the following 45 h. Hexoprenaline was administered at a dose of 3–18 μg/h dependent on contractions. Finally, patients received *Bryophyllum pinnatum* tablets 50% 4 × 2 p.o./day.

Group 2

The subsequent 15 cases (cases 16–30) received 100–200 mg indomethacin perioperatively. Instead of magnesium sulfate, atosiban was administered intraoperatively with a 6.75-mg bolus i.v. followed by 18 mg/h over 3 h and 6 mg/h for the following 45 h (=1 cycle of atosiban). Additionally, nifedipine 120 mg p.o./day was given 24 h after the fetal operation till delivery. Dependent on uterine contractions, the patient received further atosiban cycles or hexoprenaline in addition to *Bryophyllum pinnatum* tablets 50% 4 × 2 p.o./day.

After fetal MMC repair, all women were monitored in an intensive care unit (ICU) for 2 days. Analgetic management included an epidural analgesia for 3–5 days, paracetamol 4 × 1 g i.v./day, and tramadol 50–200 mg p.o./day if necessary. During the surveillance phase on the ICU, contractions were continuously registered by tocography using the IntelliSpace Perinatal information system (Philips AG Healthcare, Zurich, Switzerland) and fetal heart rate was checked by doptone (<24 GW) or CTG (>24 GW) 3 times per day. Ultrasonography was performed at least twice a day to check the amount of amniotic fluid, hematoma formation, or CMS and fetal perfusion. After transfer to our prenatal unit, contractions were monitored by tocography (<24 GW) or CTG (>24 GW) twice a day. Ultrasonography was conducted once a week. All operated women were recovered for a minimum of 4 weeks at our institution.

CMS, PPROM, and preterm deliveries within 3 weeks after fetal MMC repair as well as maternal complications from tocolysis were the major endpoints.

Statistical analysis was performed using the statistical software package SPSS version 22.0 (IBM, SPSS Inc., Chicago, IL, USA). Quantitative data are presented as mean ± standard deviation (SD) or medians with minimum and maximum values. The results of categorical variables are given as percentages. Mann-Whitney U test and χ^2 tests were used as appropriate. A p value <0.05 was considered statistically significant.

Table 1. Characteristics of patients who underwent fetal myelomeningocele repair at the Zurich Center for Fetal Diagnosis and Therapy (group 1 received tocolysis with magnesium sulfate and group 2 atosiban without magnesium sulfate)

	Group 1 (cases 1–15)	Group 2 (cases 16–30)	*p*
Gestational age at evaluation, weeks	22.2±2.1	23.2±1.9	0.17
Gestational age at fetal surgery, weeks	24.2±1.0	24.9±0.8	0.03
Maternal age, years	29.9±4.9	30.0±4.8	0.87
Nulliparous	9 (60)	9 (60)	1
Ethnicity			0.35
Caucasian	13 (87)	14 (93)	
Black	1 (7)		
Hispanic	1 (7)		
Others		1 (7)	
Body mass index	26.1±4.3	28.1±5.6	0.3
Current smoker	0	0	1
Married or living with partner	14 (93)	15 (100)	0.31
Positive family history of spina bifida	0	0	1
Previous uterine surgery	1 (7)	1 (7)	1
Cervical length, mm	42.9±5.3	40.8±4.9	0.31
Anterior placenta	8 (53)	10 (67)	0.46

Values are means ± SD or *n* (%). The only significant difference between group 1 and 2 was gestational age at surgery ($p = 0.03$).

Table 2. Rates of chorioamniotic membrane separation (CMS), premature prelabor rupture of the fetal membranes (PPROM), and delivery <3 weeks after open fetal myelomeningocele repair under tocolysis with magnesium sulfate (group 1) or atosiban without magnesium sulfate (group 2)

	Group 1 (cases 1–15)	Group 2 (cases 16–30)	*p*
CMS <3 weeks after operation, *n* (%)	1 (7)	1 (7)	1
Gestational age at diagnosis of CMS, weeks	24.0 (directly postoperatively)	25.9 (1.5 weeks after operation)	
PPROM <3 weeks after operation, *n* (%)	0	0	1
Birth <3 weeks after operation, *n* (%)	0	1 (7)*	0.31
Gestational age at birth, weeks		25.3*	

* Case with an intraoperative placental abruption and delivery directly after fetal myelomeningocele repair.

Results

Maternal characteristics of the study population are presented in Table 1. In both groups, one or no CMS or PPROM was diagnosed <3 weeks after fetal MMC repair (Table 2). GA at birth after open fetal MMC repair was comparable in both groups (Table 3).

One patient (7%) of group 2 delivered <3 weeks after fetal MMC repair. Here, an intraoperative placental abruption occurred towards the end of the operation. This event was unrelated to tocolysis. Whether it took place due to massive amnioreduction or uterine manipulation during fetal positioning remains speculative. Therefore, the fetus was delivered during the intervention at GA 25.3 weeks. The baby girl finally went home with no major

Table 3. Gestational age at birth after open fetal myelomeningocele repair under tocolysis with magnesium sulfate (group 1) or atosiban without magnesium sulfate (group 2)

	Group 1 (cases 1–15)	Group 2 (cases 16–30)	*p*
Gestational age at birth, weeks	35.9±1.4	35.2±3.2	0.43
<30 weeks, *n* (%)	0	1 (7)*	0.31
30–34 weeks, *n* (%)	4 (27)	3 (20)	0.67
35–36 weeks, *n* (%)	5 (33)	6 (40)	0.71
≥37 weeks, *n* (%)	6 (40)	5 (33)	0.71

* Case with an intraoperative placental abruption and delivery directly after fetal myelomeningocele repair.

neurologic deficit and no prematurity-associated sequelae except for bilateral retinopathy that responded well to laser therapy. This case of an intraoperative placental abruption was excluded for the comparison of the tocolytics. In both groups, postoperative contractions were successfully suppressed.

All women of group 1 showed an oftentimes marked electrolyte imbalance during the magnesium sulfate administration with serum levels of 3.2 ± 0.4 mmol/L. All women had a hypocalcemia with total calcium serum levels of 1.5 ± 0.2 mmol/L. One woman with the lowest calcium level of 1.13 mmol/L – her maximal magnesium level was 3.0 mmol/L – showed carpopedal spasms which needed treatment with calcium i.v. Potassium or sodium serum levels of these women were 3.4 ± 0.3 mmol/L or 137 ± 1.9 mmol/L, respectively. Transient hypokalemia or hyponatremia was present in 5 (33%) or 6 (40%) women, respectively. Objectively, severe lethargy was found in all women during magnesium sulfate therapy. Subjectively, all patients complained about feeling severely ill for 2–3 days ("like run over by a truck").

The last patient of group 1 (case 15) developed 4 short episodes of a third-degree atrioventricular block (AV block III°) within the first 3 days after fetal surgery, so that she was monitored for a total of 8 days in the ICU. Her maximum magnesium blood level was 3.05 mmol/L. After the first AV block III° episode, occurring 11 h after fetal surgery, magnesium sulfate was stopped. Phosphate and calcium were substituted in order to correct her electrolyte imbalance. All further assessments including echocardiography, 48 h-ECG, and heart MRI for exclusion of an arrhythmogenic right ventricular cardiomyopathy showed normal results. Further course of pregnancy was uneventful till delivery after PPROM with contractions at GA 32.7 weeks.

The women of group 1 did not receive statistically significantly more indomethacin (117 ± 31 mg) when compared with the women of group 2 (100 ± 0 mg) ($p = 0.23$).

There were no side effects whatsoever attributable to atosiban therapy. All women of group 2 were completely awake within the first hours after open fetal MMR repair and none uttered similar complaints as those of the patients of group 1.

Discussion

This study compared magnesium sulfate with atosiban for perioperative tocolysis in the context of open fetal surgery for spina bifida. The main endpoints of this prospective cohort study were tocolytic efficacy and maternal side effects.

In the global picture, we found similar rates of CMS, PPROM, and delivery within 3 weeks after fetal MMC repair in both groups, indicating that both tocolytic regimens are similar if not identical regarding uterine efficacy.

Yet, under magnesium sulfate, all women exhibited an oftentimes marked electrolyte imbalance, lethargy, and feelings of being sick. One woman developed severe and potentially dangerous episodes of an AV block III° within the first 3 days after fetal surgery, almost certainly triggered by a magnesium-induced marked electrolyte imbalance, since other arrhythmogenic factors could be ruled out. In sharp contrast, all patients in the atosiban group were completely free from any measurable side effects, and they uttered no feelings of being sick whatsoever.

Maternal side effects from treatment with high-dose magnesium sulfate for preterm labor are well known [5]. Of 456 women, 417 (91%) experienced side effects, with severe symptoms in 24 women (5.3%). Of these 24 women, 23 (5% of the total cohort) had pulmonary edema and one developed tachyarrhythmia while on magnesium. All were transferred to the ICU [5]. Also, one should be aware of possible cardiopulmonary drug interactions among pregnant women who receive magnesium sulfate. Thus, cardiac arrest was documented in 5 of 53 (9.3%) women who additionally received furosemide [6]. In our case of an AV block III°, no additional drug interaction could be identified, but the electrolyte imbalance was considered to be the trigger as other arrhythmogenic causes were absent.

As the best maternal safety profile was shown for atosiban when compared with magnesium sulfate, beta-mimetics, indomethacin, or calcium channel blockers [7, 8], and based on our own experience reported here, we strongly recommend that magnesium sulfate should not be used as a short-term tocolytic anymore. Instead, atosiban seems to be the most appropriate choice.

In contrast to Europe, there is no approved tocolytic in the US to treat preterm labor. Thus, Klauser et al. in 2014 [9] stated that clinicians in the US should use the medication that yielded the best results with the lowest rate of maternal or neonatal side effects. Elliot and Morrison in 2013 [10] explicitly criticize that the FDA has blocked the use of atosiban in the US although it remains available, and is routinely used, in the rest of the world.

The use of magnesium sulfate as a tocolytic agent is still controversial [7]. In a Cochrane analysis on giving birth within 48 h after trial entry, no significant differences were seen between women who received magnesium sulfate for tocolysis and women who did not [11]. Furthermore, in the group treated with magnesium sulfate compared to women receiving antenatal placebo or no alternative tocolytics, a minimally increased risk of fetal, neonatal, or infant death was seen (RR 4.56, 95% CI 1.00–20.86; 2 trials, 257 babies). Thus, the authors concluded that, in contrast to its effect on neuroprotection, magnesium sulfate is ineffective at delaying birth or preventing preterm birth, has no apparent advantages, and its use for this indication may be associated with an increased risk of total fetal, neonatal, or infant mortality [11]. Moreover, the FDA recently changed the classification of magnesium sulfate from category A to D for concern of fetal and neonatal bone demineralization and fractures associated with long-term in utero exposure to magnesium sulfate [12]. Therefore, the FDA advised against the use of magnesium sulfate injections for more than 5–7 days to stop preterm labor. Finally, the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine stated in January 2016 that they still support the short-term use of magnesium sulfate for prevention and treatment of seizures in women with preeclampsia or eclampsia, fetal neuroprotection below 32 weeks, and short-term tocolysis for up to 48 h in order to reach the time for fetal lung maturation [13].

In this study, an incidence of 7% CMS within 3 weeks after fetal surgery was detected in both groups, apparently independent of which tocolytic regimen was used. CMS is known to be a significant risk factor for subsequent development of PPROM and preterm delivery [14, 15]. Johnson et al. [14] described recently that CMS ≤34 weeks occurred in 33% and at a mean of 3.6 days after fetal surgery. Only shorter duration of postoperative magnesium sulfate medication (CMS: 21 ± 3.6 h vs. without CMS: 22.5 ± 3.2 h) was associated with an increased risk of CMS ≤34 weeks, but it was no longer significant after adjusting for the respective clinical center [14].

No PPROM within 3 weeks after fetal surgery was found in this study. However, in the post-MOMS experience, 4 neonatal demises were mentioned where women had PPROM or preterm labor within 2 weeks of MMC repair at 22–24 weeks [16]. Of these, 2 were previable, in 1 case, comfort care was provided per parental decision, and in 1 case, support was withdrawn due to severe prematurity [16]. Thus, it is important to prevent PPROM or preterm labor by tocolytics as vigorously and as early as possible. It has been shown in an experimental study by Perrini et al. in 2013 [17] that contractions increase the risk of PPROM. They investigated the effect of repeated mechanical stretching on the rupture and deformation properties of fetal membranes. Already 10 stretching cycles of the fetal membranes, representative of mean physiological contractions, reduced the work to rupture. Second harmonic generation microscopy, which is based on a nonlinear optical effect and which offers visualization of viable cells and their tissue structures and function, found that repeated mechanical loading of fetal membranes affected the integrity of the amnion-chorion interface with an altered collagen structure [18].

In conclusion, this study produced evidence that the perioperative use of atosiban versus magnesium sulfate resulted in a similar short-term uterine outcome. While magnesium sulfate was associated with increased and potentially severe maternal complications, atosiban was completely free of side effects. These results strongly suggest using atosiban instead of magnesium sulfate in the context of open fetal surgery for spina bifida.

Disclosure Statement

All authors declare no conflicts of interest.

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