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Oxytocin exposure in women with postpartum hemorrhage secondary to uterine atony

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Abstract

Objective—To determine if women with severe postpartum hemorrhage (PPH) secondary to uterine atony received greater amounts of oxytocin compared to women without PPH.

Study Design—Subjects with both severe PPH, defined as having received a blood transfusion, and PPH secondary to uterine atony were compared to matched controls. Total oxytocin exposure was calculated as the area under the concentration curve (mUnits/min*mins). Variables were compared using paired t-test, chi-square and logistic regression.

Results—Women with severe PPH had a mean oxytocin area under the curve (AUC) of 10,054 mU compared to 3762 mU in controls ($p<0.001$). After controlling for race, BMI, admission hematocrit, induction status, magnesium therapy, and chorioamnionitis using logistic regression, oxytocin AUC continued to predict severe PPH.

Conclusion—Women with severe PPH secondary to uterine atony were exposed to significantly more oxytocin compared to matched controls.

Keywords

desensitization; oxytocin; oxytocin receptor; postpartum hemorrhage; uterine atony

INTRODUCTION

Postpartum hemorrhage (PPH) is a significant source of maternal morbidity and mortality and remains the most common cause of maternal death worldwide.[1, 2] In the United States, hemorrhage is second only to embolism as the most common cause of maternal mortality.2 Studies have described risk factors for PPH including prolonged third stage of labor,

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preeclampsia, episiotomy, history of prior PPH, multiple gestation, lacerations, augmented labor, second-stage arrest disorders, marcrosomia, chorioamnionitis, general anesthesia, Hispanic ethnicity and operative vaginal delivery.[3-5] Clark et al found uterine atony to be the most frequent indication for emergency hysterectomy in their obstetric population, representing 43% of the cases.[6] A recent multi-center study conducted by the Maternal-Fetal Medicine Unit (MFMU) network of the NICHD found that subjects with uterine atony following primary cesarean delivery were exposed to a longer duration of oxytocin compared to women without uterine atony. They also identified other associations with uterine atony including multiple gestation, maternal Hispanic race, birthweight >4500g and clinically diagnosed chorioamnionitis. Due to the strong association of oxytocin duration greater than 12 hours in their study, the authors elected not to include this variable in the multivariable analysis for predictors of uterine atony.[7] Therefore, it is unclear if this association would have held after controlling for the other independent risk factors. Regardless, prolonged oxytocin exposure is likely an important factor in the pathophysiology of uterine atony.

Oxytocin is a peptide that mediates its action through the oxytocin receptor (OXTR). The OXTR belongs to the family of G protein-coupled receptors (GPCRs), and like other GPCRs, undergoes rapid internalization in the setting of persistent agonist stimulation, which can limit the physiological actions of oxytocin.[8] Prolonged oxytocin treatment leads to OXTR desensitization, thereby limiting further oxytocin-mediated contraction responses. 9 Whether these molecular events lead to the clinical findings of dysfunctional labor patterns or uterine atony in the setting of prolonged oxytocin stimulation is unclear.

We conducted this case-control study to test the hypothesis that prolonged oxytocin exposure increases the risk for PPH secondary to uterine atony.

MATERIALS AND METHODS

Study design

This was a case-control study approved by the Duke University Medical Center Institutional Review Board (IRB# 6066-04-6ROER and IRB# e00011058) and was conducted to test the hypothesis that women with severe PPH secondary to uterine atony received greater amounts of oxytocin compared to controls.

Study population

Cases were defined as a subject with an International Classification of Diseases version 9 (ICD-9) code of 666.0X, 666.1X and 666.2X for PPH who also received a blood transfusion. The medical records of women delivering at Duke University Medical Center over the five-year period between January 2000 and December 2004 with an ICD-9 code for PPH were reviewed. We then determined the etiology of PPH and defined cases in this study as women with severe PPH whose etiology for PPH was uterine atony. Next, a matched control was identified for each case. The controls selected were the next successive delivery following its paired case, matched for age (within 5 years), parity (nulliparous versus multiparous) and mode of delivery (vaginal, cesarean delivery before labor, cesarean delivery during labor).

Procedures

The medical records for cases and controls were reviewed by one of three physician study staff (CAG, MJP, LNCJ). The study variables collected were subject's age, race, height, weight, gravidity, parity, number of fetuses, gestational age at delivery, history of PPH with a previous delivery, type of delivery, need for induction, augmentation with oxytocin during labor, estimated blood loss at the time of delivery, pre-labor hematocrit, first hematocrit

following delivery, etiology of PPH (placental abruption, abnormal placentation, uterine atony, laceration), infant birthweight, maternal blood type, maternal medical conditions, type and quantity of blood product received, maximum maternal temperature during labor or postpartum (marker for chorioamnionitis or endometritis, respectively), and medications received or procedures conducted as treatment for PPH. Body mass index (BMI) was calculated based on the subject's height and the first weight noted in her obstetric record.

Oxytocin exposure was calculated as the area under the curve. The time at which oxytocin infusion was initiated was recorded and the time and dose of each dose change was also noted. A graph of oxytocin dose (mUnits/min) versus time (minutes) was constructed for each subject. The area under the oxytocin dose curve (AUC, mUnits/min * min) for each subject was calculated using GraphPad Prism for Macintosh (version 5.0a, GraphPad Software, San Diego, CA, USA, www.graphpad.com). The time from oxytocin initiation to delivery, total time of oxytocin treatment, maximal oxytocin dose, time from maximal oxytocin dose to delivery, time from oxytocin discontinuation and oxytocin dose at delivery were also recorded.

Statistical analysis

Continuous variables were compared between cases and matched controls using a paired t-test and a paired Wilcoxon Sign-Rank test. Categorical variables were compared using chi-square or Fisher's exact tests where appropriate. Logistic regression models were constructed for the outcome severe PPH to identify potential confounding variables with odds ratios (OR) and 95% confidence intervals (95% CI). To compute odds ratios for categorical variables with more than two outcomes, multiple comparisons for two outcomes were performed. Significance for all analyses was defined as a p-value < 0.05. All statistical analysis was conducted using JMP for Macintosh (JMP version 8.0.1, SAS Institute, Inc, Cary, NC, USA, www.jmp.com).

RESULTS

There were 12,476 deliveries at Duke University Medical Center over the five-year period from January 2000 to December 2004. Six-hundred seventy-one (5.4%) had an ICD-9 diagnosis of PPH. Of these 671 subjects, there were 109 deliveries to 109 unique subjects who required a blood transfusion, and were therefore, classified as subjects with severe PPH. Of these 109 subjects, the primary etiology of PPH was lacerations in 13%, retained products in 11%, placenta previa in 8%, and placenta accreta in 1%. In fifty-four subjects (50%) uterine atony was identified as the primary etiology of PPH.

The cases were similar to the controls with respect to maternal age, BMI and percent of subjects who were nulliparous, although there was a trend toward lower BMI in the cases (p=0.054). The cases were more likely to be of Hispanic ethnicity and the controls were more likely to be Caucasian or African American. Cases presented with a lower hematocrit at the time of admission (33.3% vs. 35.6%, p<0.001) compared to controls. There were no differences in other maternal characteristics including substance abuse, smoking, history of PPH, use of anticoagulation during the pregnancy, diabetes, chronic hypertension or sickle cell trait between cases and controls (Table 1).

Table 2 lists obstetric characteristics of cases and controls. The cases and controls had similar modes of delivery, as this was a criterion for matching. There were no differences in type of obstetric laceration, gestational age at delivery or birthweight. Cases had a larger estimated blood loss (EBL) compared to controls (1199 ml vs. 517 ml, p<0.001). Cases also had a greater change in hematocrit (14.9% vs. 5.8%, p<0.001). Cases were more likely to have had preeclampsia and to have received magnesium therapy compared to controls.

Alhough cases were more likely to have had endometritis, there were no differences in rates of chorioamnionitis compared to controls (Table 2).

The oxytocin treatment variables are listed in Table 3. Cases were exposed to significantly more oxytocin as measured by AUC compared to controls (10,054 mU vs. 3762 mU, $p<0.001$). The mean time of initiation of oxytocin to delivery and overall oxytocin exposure time was greater in cases when compared to controls (684 mins vs. 330 mins, $p<0.001$ and 628 mins vs. 294 mins, $p<0.001$, respectively). Cases also had a higher maximal oxytocin dose during labor when compared with controls (16.6 mU/min vs. 7.0 mU/min, $p<0.001$). Cases had a higher oxytocin dose at time of delivery compared to controls (5.6 mU/min vs. 2.5 mU/min, $p=0.045$), although there were no differences in time from maximal oxytocin dose to delivery and time from oxytocin discontinuation to delivery between cases and controls. Finally, there were no differences in the percent of cases receiving oxytocin at the time of delivery or the percent of cases for which the maximal oxytocin dose during labor was at the time of delivery compared to controls. (Table 3).

The cases and controls were matched by mode of delivery; vaginal, cesarean delivery before labor, cesarean delivery during labor, but the indication for cesarean delivery was different between cases and controls. Cases were more likely to have had a cesarean delivery for the indication of arrest of cervical dilatation while controls were more likely to have had a cesarean delivery for non-reassuring fetal status (Table 4).

All cases and controls received intravenous oxytocin immediately following delivery of the placenta per protocol in an attempt to prevent uterine atony. All cases received uterotonic agents to treat uterine atony and many received more than one agent. The uterotonic agents methergine, prostaglandin F2-alpha and misoprostol were the most commonly used agents. Sixty-three percent of cases received methergine, 68.5% of cases received prostaglandin F2-alpha and 31.5% of cases received misoprostol. In addition, uterine curettage was performed in 13% of the cases and a B-Lynch uterine brace suture was placed in another 13% of cases. Three control subjects (5.6%) received uterotonic agents which included methergine and/or misoprostol.

A logistic regression model was constructed for the outcome of severe PPH. Table 5 lists the unadjusted and adjusted odds ratios (ORs) for the predictors oxytocin AUC, oxytocin maximal dosing, race, maternal BMI, admission hematocrit, induction status, preeclampsia, magnesium therapy, and chorioamnionitis. All predictors except maternal BMI and chorioamnionitis were found to significantly predict PPH. Multivariate logistic regression demonstrated that oxytocin AUC continued to predict PPH while controlling for independently significant variables and clinically relevant variables ; race, BMI, admission hematocrit, induction status, magnesium treatment, and chorioamnionitis. Endometritis was not included in the model since there were no cases of endometritis among the control subjects. Preeclampsia was not included in the final model since all subjects with preeclampsia received magnesium.

COMMENT

Oxytocin exposure has previously been identified as a risk factor for uterine atony although others have not attempted to quantify the amount of oxytocin that may increase the risk. Our study is unique in that it quantifies the amount of oxytocin received in a cohort of subjects with severe PPH secondary to uterine atony and compares this to a matched control group. We demonstrated that women with severe PPH secondary to uterine atony were exposed to greater amounts of oxytocin as measured by area under the oxytocin dose curve compared to matched controls. In addition, women with severe PPH secondary to uterine atony were also

exposed to oxytocin for a longer duration of time compared to controls and to higher maximal oxytocin dosing. Using logistic regression analysis, we were able to control for other variables that were shown to be associated with severe PPH secondary to uterine atony. This analysis continued to demonstrate that oxytocin AUC was able to predict PPH cases.

The molecular mechanisms of OXTR signaling may help to explain the clinical finding of uterine atony associated with prolonged oxytocin infusions. The OXTR is a member of the GPCR family that, like other GPCRs, undergoes molecular desensitization following activation. Upon agonist binding to the OXTR, the receptor rapidly internalizes and uncouples from its associated G protein, thereby limiting further oxytocin signaling until the receptor recycles back to the cell membrane.[8, 10] Therefore, prolonged oxytocin treatment leads to OXTR desensitization, thereby limiting further oxytocin-mediated contraction responses.[9] We propose that prolonged oxytocin treatment leads to OXTR desensitization that interferes with uterine contractility, leading to uterine atony and PPH.

The odds ratios for the association of oxytocin AUC with severe PPH were reported for a 5000 mU increase in oxytocin AUC, rather than dichotomizing oxytocin AUC into high and low levels or to report the odds ratio for an increase of 1 mU in oxytocin AUC. We believed that reporting the odds ratio over a larger increase in AUC would have more meaningful clinical implications. While controlling for race, BMI, admission hematocrit, induction status, magnesium therapy, and chorioamnionitis, an increase in 5000 mU of oxytocin increases the odds for severe PPH by 1.62. An increase in oxytocin AUC of 5000 mU is equivalent to a woman receiving an oxytocin infusion at 20 mU/min (a typical maximal infusion at many centers) for 4.2 hours.

There were a wide range in mean oxytocin AUC values seen in both women with severe PPH and controls as exhibited by the large standard deviations around the mean values. Because of this, the analysis was repeated using a non-parametric paired Wilcoxon Sign-Rank test, which gave p-values that were similar to those listed here. The finding that there is a wide spread in oxytocin AUC among women with severe PPH is not surprising. Previous work has demonstrated that the serum level of oxytocin that is required for adequate contraction activity is highly variable among women. Therefore, the oxytocin dose that a woman would receive in attempt to achieve delivery would likely also be highly variable.[11, 12]

In our study, control subjects were matched to cases by age, parity and mode of delivery. Mode of delivery was classified as vaginal, cesarean delivery before labor and cesarean delivery during labor. The indication for cesarean delivery in labor differed between cases and controls. Control subjects were more likely to have a cesarean delivery during labor for the indication of non-reassuring fetal status while case subjects were more likely to have a cesarean delivery for arrest of cervical dilatation. This finding occurred despite the fact that there were no differences in birthweight between cases and controls.

All of the cases in this study received uterotonic agents indicated for the treatment of uterine atony. These agents included methergine, prostaglandin F2-alpha and misoprostol. This suggests that the cases were correctly identified as having uterine atony. Our study also identified other associations that were predictive of PPH. These included Hispanic ethnicity, admission hematocrit, preeclampsia, magnesium therapy and endometritis. Other groups have noted an association of Hispanic ethnicity with PPH.[3, 7] In our study, this association held while controlling for birthweight and mode of delivery. Preeclampsia has also been identified as an independent risk factor for PPH by other groups.[3, 4] At the time of our study, most preeclamptic subjects received magnesium therapy, which has also previously

been identified as a risk factor of PPH. It is unclear if preeclampsia alone in our study was predictive of PPH given that all subjects with preeclampsia received magnesium therapy. Lastly, other groups have identified chorioamnionitis as a risk factor for uterine atony. We did not see a difference in clinical chorioamnionitis between cases and controls, although cases did have higher rates of endometritis. It is possible, that chorioamnionitis was inaccurately recorded in the patient's medical record.

Given the finding that increased oxytocin dosing is associated with uterine atony and PPH, methods to decrease oxytocin utilization may decrease these adverse events. Daniel-Spiegel et al demonstrated that in women undergoing induction of labor, that oxytocin infusions can be discontinued once active labor is achieved (defined as 5 cm in their study) without affecting overall time to delivery or mode of delviery.[13] Clark et al demonstrated that adoption of a conservative checklist oxytocin protocol for women undergoing labor induction or augmentation, led to decreased oxytocin utilization without affecting cesarean delivery rates.14 Both of these protocols decrease the amount of oxytocin exposure in the latter parts of labor and may, therefore, decrease the risk for OXTR desensitization and uterine atony. Unfortunately, neither of these groups analyzed blood loss when comparing the two various oxytocin protocols.

Our study is limited in that we identified cases by ICD-9 coding which may have missed subjects with PPH. In addition, our study was designed as a retrospective case-control study. We, therefore, relied on data being accurately recorded in the medical record. All cases, however, were truly severe, as defined by receiving transfusion and all identified subjects were accurately identified as having had PPH secondary to uterine atony.

Uterine atony is the most common etiology of severe PPH at our institution. Worldwide, PPH is a significant source of maternal morbidity and mortality. We demonstrated that oxytocin exposure is a significant independent risk factor of severe PPH secondary to uterine atony. This finding supports the molecular mechanisms involved in OXTR desensitization in the setting of prolonged oxytocin desensitization leading to decreases in oxytocin-mediated function. Protocols that decrease the amount of oxytocin that patients receive may decrease the incidence of PPH secondary to uterine atony.

CONDENSATION

Women with postpartum hemorrhage secondary to uterine atony received greater amounts of oxytocin as measured by area under the concentration curve compared to controls.

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Table 1

Subject Characteristics

Characteristic	PPH atony (n=54)	Control (n=54)	*p*-value[b]
Age, years [a]	27.6 ± 7.3	27.2 ± 7.3	0.207
Nulliparous, n (%)	33 (61)	33 (61)	NS
Body mass index, kg/m^2 [a]	29.9 ± 5.6	32.2 ± 6.8	0.054
Race/Ethnicity, n (%)			0.010
Caucasian	14 (25.9)	21 (40.4)	
African American	15 (27.8)	23 (44.2)	
Hispanic	21 (38.9)	6 (11.5)	
Asian	2 (3.7)	2 (3.7)	
Other	2 (3.7)	0 (0)	
Admission hematocrit, % [a]	33.3 ± 4.0	35.6 ± 3.9	<0.001
Substance Abuse, n (%)	1 (1.8)	1 (1.8)	1
Smoking, n (%)	6 (11.1)	8 (14.8)	0.567
History of PPH, n (%)	2 (3.7)	1 (1.8)	0.558
Anticoagulation in pregnancy, n (%)	2 (3.7)	1 (1.8)	0.558
Diabetes, n (%)	5 (9.3)	1 (1.8)	0.09
Chronic hypertension, n (%)	3 (5.6)	2 (3.7)	0.647
Sickle Cell Trait, n (%)	3 (5.7)	1 (1.8)	0.299

[a] Values are mean ± SD

[b] Paired t-test for continuous variables; Chi-square or fisher's exact test for categorical variables.

Table 2

Obstetric and Medical Characteristics

Characteristic	PPH atony (n=54)	Control (n=54)	*p*-value[b]
Mode of delivery, n (%)			1.0
Spontaneous vaginal delivery	16 (29.6)	16 (29.6)	
Operative vaginal delivery	3 (5.6)	3 (5.6)	
Cesarean delivery in labor	25 (46.3)	25 (46.3)	
Cesarean delivery without labor	10 (18.5)	10 (18.5)	
Lacerations, n (%)			0.473
None	40 (74.1)	46 (85.2)	
$1^{st}/2^{nd}$	9 (16.7)	6 (11.1)	
$3^{rd}/4^{th}$	2 (3.8)	1 (1.9)	
Other	3 (5.6)	1 (1.9)	
Gestational age at delivery, weeks [a]	38.8 ± 2.6	38.3 ± 4.4	0.475
Birth weight, g [a]	3352 ± 806	3245 ± 582	0.431
Estimated blood loss, ml [a]	1199 ± 785	517 ± 236	<0.001
Change in Hematocrit, % [a]	14.9 ± 4.8	5.8 ± 3.9	<0.001
Induction status, n (%)	22 (40.7)	13 (24.1)	0.063
Preeclampsia, n (%)	18 (33.3)	5 (9.3)	0.001
Magnesium treatment, n (%)	14 (25.9)	5 (9.3)	0.008
Chorioamnionitis, n (%)	6 (11.1)	3 (5.6)	0.296
Endometritis, n (%)	4 (7.4)	0 (0)	0.017

[a] Values are mean ± SD

[b] Paired t-test for continuous variables; Chi-square or fisher's exact test for categorical variables.

Table 3

Oxytocin treatment measurements

Characteristic	PPH atony (n=54)	Control (n=54)	*p*-value
Total oxytocin dose, AUC, mU [a]	10054 ± 11340	3762 ± 7093	<0.001
Time oxytocin start to delivery, min [a]	684 ± 593	330 ± 526	<0.001
Total time of oxytocin infusion, min [a]	628 ± 574	294 ± 467	<0.001
Oxytocin max dose, mU/min [a]	16.6 ± 14.7	7.0 ± 10.9	<0.001
Time oxytocin max dose to delivery, min [b]	109 ± 38	87 ± 38	0.64
Time oxytocin discontinuation to delivery, min [b]	37 ± 11	31 ± 11	0.58
Oxytocin dose at delivery, mU/min [a]	5.6 ± 9.9	2.5 ± 6.6	0.045
Subjects with oxytocin infusion on at delivery, n (%) [c,d]	19 (50)	9 (45)	0.72
Subjects with maximal oxytocin infusion on at delivery, n (%) [c,d]	10 (26.3)	7 (35)	0.49

AUC, area under the curve

[a] Values are mean ± SD, *p*-value for paired t-test

[b] Values are mean ± SE (paired test). These characteristics calculated only for those paired subjects receiving oxytocin.

[c] These characteristics calculated for all subjects receiving oxytocin, PPH atony group n=38, control n=20

[d] Comparison made with chi-square

Table 4

Cesarean delivery indications

Characteristic	PPH atony N=35	Control N=35	p-value[a]
Cesarean indication, n (%)			0.039
Non-reassuring fetal status	4 (11.4)	10 (26.5)	
Arrest dilatation	20 (57.1)	6 (17.6)	
Arrest descent	0 (0)	1 (2.9)	
Repeat elective	3 (8.6)	5 (14.7)	
Multiples	4 (11.4)	4 (11.4)	
Breech	1 (2.9)	3 (8.8)	
Fetal macrosomia	1 (2.9)	2 (5.7)	
Maternal indications	1 (2.9)	2 (5.7)	
Maternal HIV infection	0 (0)	2 (5.9)	
History of myomectomy	1 (2.9)	0 (0)	

[a]Chi-square or fisher's exact test for categorical variables.

Table 5

Unadjusted and adjusted logistic regression analysis for outcome PPH secondary to uterine atony

Predictor	**Denom/Numerator of OR**	**Unadjusted OR (95% CI) *p*-value**	**Adjusted OR (95% CI) *p*-value**
Oxytocin AUC	5000 mU increase	1.47 (1.17, 1.93) <0.001	1.58 (1.05, 2.57) 0.026
Race	Hispanic/Caucasian	5.25 (1.69, 16.39) 0.005	1.36 (0.41, 5.59) 0.540
BMI	1-unit increase	0.94 (0.88, 1.01) 0.11	0.97 (0.89, 1.04) 0.449
Admission Hematocrit	1-unit increase	0.86 (0.77, 0.95) 0.004	0.05 (0.002, 0.93) 0.044
Induction status	Yes/No	2.17 (0.95, 5.06) 0.063	1.16 (0.34, 3.78) 0.803
Preeclampsia	Yes/No	4.90 (1.66, 14.43) <0.001	*
Magnesium therapy	Yes/No	3.43 (1.14, 10.34) <0.001	1.17 (0.27, 5.34) 0.832
Chorioamnionitis	Yes/No	2.10 (0.93, 10.50) 0.30	4.38 (0.42, 58.5) 0.217

* Not included in adjusted analysis since preeclampsia and magnesium therapy are dependent on each other