Published in final edited form as:

Am J Obstet Gynecol. 2015 May ; 212(5): 642.e1–642.e7. doi:10.1016/j.ajog.2015.01.008.

Second Line Uterotonics and The Risk of Hemorrhage-Related Morbidity

Alexander J. Butwick, MBBS, FRCA, MS¹, Brendan Carvalho, MB, ChB, FRCA¹, Yair J Blumenfeld, MD², Yasser Y. El-Sayed, MD², Lorene M Nelson, MS, PhD³, and Brian T. Bateman, MD, MSc⁴

¹Department of Anesthesia, Stanford University School of Medicine, Stanford California

²Department of Obstetrics and Gynecology, Stanford University School of Medicine, Stanford California

³Department of Health Research Policy, Stanford University School of Medicine

⁴Department of Anesthesiology, Critical Care Medicine, and Pain Medicine, Massachusetts General Hospital, Boston Massachusetts

Abstract

Objective—Uterine atony is a leading cause of postpartum hemorrhage (PPH). Although most cases of PPH respond to first line therapy with uterine massage and oxytocin administration, second line uterotonics including methylergonovine and carboprost are integral for the management of refractory uterine atony. Despite their ubiquitous use, it is uncertain whether the risk of hemorrhage-related morbidity differs in women exposed to methylergonovine or carboprost at Cesarean delivery (CD).

Study Design—We performed a secondary analysis using the Maternal-Fetal Medicine Units Network Cesarean Registry. We identified women who underwent CD and received either methylergonovine or carboprost for refractory uterine atony. The primary outcome was hemorrhage-related morbidity defined as intraoperative or postoperative red blood cells transfusion or the need for additional surgical interventions including uterine artery ligation,

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Correspondence Address: Dr. A. Butwick, Department of Anesthesiology (MC:5640), Stanford University School of Medicine, 300 Pasteur Drive, Stanford, California 94305, Fax: 650-735-8544, ajbut@stanford.edu.

Presentation: Data from this manuscript was presented as an oral presentation at the 34th Annual Meeting of the Society of Obstetric Anesthesia and Perinatology, Toronto, Canada, May 5–9, 2014.

Disclaimer: We acknowledge the assistance of NICHD, the MFMU Network, and the Protocol Subcommittee in making the database available on behalf of the project. The contents of this report represent the views of the authors and do not represent the views of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network or the National Institutes of Health.

Disclosures of Conflict of Interest: The authors report no conflict of interest.

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hypogastric artery ligation, or peripartum hysterectomy for atony. We compared the risk of hemorrhage-related morbidity in those exposed to methylergonovine vs. carboprost. Propensity-score matching was used to account for potential confounders.

Results—The study cohort comprised 1,335 women; 870 (65.2%) women received methylergonovine and 465 (34.8%) women received carboprost. After accounting for potential confounders, the risk of hemorrhage-related morbidity was higher in the carboprost group than the methylergonovine group (RR = 1.7; 95% CI = 1.2 – 2.6).

Conclusion—In this propensity-score matched analysis, methylergonovine was associated with reduced risk of hemorrhage-related morbidity during CD compared to carboprost. Based on these results, methylergonovine may be a more effective second line uterotonic.

Keywords

Uterine Atony; Cesarean Section; Morbidity; Hemorrhage

INTRODUCTION

Postpartum hemorrhage is recognized as a leading cause of maternal mortality and morbidity worldwide.¹ Data from epidemiologic studies indicates that the incidence of postpartum hemorrhage (PPH) has been steadily increasing in a number of well-resourced countries, with uterine atony identified as the main explanatory factor for this increase.^{2–5} The increase in rates of uterine atony has major clinical and public health relevance as atonic PPH has been linked to major hemorrhage-related morbidities, notably peripartum hysterectomy and massive transfusion.^{6, 7}

Uterine massage and oxytocin administration are routinely performed prophylactically for the prevention of post-delivery uterine atony. Although pharmacologic prophylaxis with oxytocin is associated with a reduced risk of PPH compared to no uterotonics,⁸ refractory uterine atony can occur when the uterus fails to adequately contract after administration of oxytocin and uterine massage. In the setting of refractory uterine atony, second line uterotonic agents, such as methylergonovine maleate (Methergine) and carboprost (Hemabate) are recommended by the American College of Obstetricians and Gynecologists and the Royal College of Obstetrics and Gynaecology^{9, 10} and recent data suggest both agents are widely used in contemporary obstetric practice.¹¹ Previous studies have compared methylergonovine vs. carboprost as *prophylaxis* against uterine atony and PPH in women undergoing vaginal delivery.^{12–15} However, data regarding the comparative effectiveness of these agents for uterine atony refractory to oxytocin are lacking, particularly in the setting of cesarean delivery. Because refractory uterine atony during cesarean delivery is often unanticipated, prospective randomized clinical investigations of methylergonovine and carboprost in this setting are logistically challenging to perform. However, the availability of large clinical datasets provides the opportunity to examine outcomes with a low prevalence, such as refractory uterine atony during cesarean delivery. The objective of this study was to examine whether the risk of hemorrhage-related morbidity differs between women who receive methylergonovine compared to carboprost during cesarean delivery.

MATERIALS AND METHODS

Data source

Data were obtained from the Cesarean Registry which contains data collected for a multicenter study by the National Institute of Child Health and Human Development Maternal-Fetal Medicine Units (MFMU) Network.¹⁶ Details of this study have been previously summarized.¹⁶ Between 1999 and 2000, investigators collected data from women who underwent delivery by primary cesarean delivery, repeat cesarean delivery or vaginal delivery after cesarean delivery and who delivered infants ≥ 20 weeks or ≥ 500 grams at 19 academic centers in the United States. Between 2001 and 2002, only women who underwent repeat cesarean delivery or vaginal birth after cesarean delivery and who delivered infants ≥ 20 weeks or ≥ 500 grams were enrolled. Patient and hospital identifiers were removed by the MFMU. Trained research nurses manually abstracted data from patients' medical records. Data was submitted to a biostatistical coordinating center where audits were regularly performed to assess data quality. For the original study, ethics committees in each participating center approved the study protocol; informed consent was not required as data collection consisted only of abstraction from the medical records. Because of the deidentified data within the Cesarean Registry dataset, this secondary analysis received a waiver of exemption by the Stanford University institutional review board.

Study Cohort

For our study cohort, we selected women who had undergone cesarean delivery who received either methylergonovine or carboprost, but not both, for the treatment of uterine atony. Trained nurses abstracted relevant information about the presence of uterine atony and the administration of second line uterotonics from medical records within each study site. No specific data on prophylactic regimens used at study sites were available in the Cesarean Registry. However, previously published data from Rouse et al. indicates that oxytocin was routinely used as prophylaxis at 13 study sites, with 12 sites using 20 U oxytocin/L infused at 125–250 mL/hr.¹⁷ Women who had abnormal placentation were excluded from our analysis. We also excluded women with any medical or pregnancy related hypertensive disorder or asthma as these patients would not have been eligible for receiving either methylergonovine or carboprost. After accounting for these exclusions, the final study cohort comprised 1,335 women (Figure 1).

Study Outcomes

The primary study outcome was hemorrhage-related morbidity, which was defined by the presence of at least one of the following: intraoperative or postoperative red blood cells (RBC) transfusion, uterine artery ligation or hypogastric artery ligation, or hysterectomy for the indication of uterine atony. These medical and surgical interventions have been previously defined as markers for severe atonic PPH¹⁸ and in prior studies were demonstrated to be important indicators of severe, hemorrhage-related obstetric morbidity during delivery hospitalizations.^{19–23} In addition, these non-pharmacological interventions have been described in treatment pathways for atonic PPH unresponsive to second line uterotonic agents.^{24, 25}

Covariates

Based on available data in the Cesarean Registry, three classes of potential confounders were included in our analysis: maternal demographics, obstetric characteristics, and perinatal factors. Maternal demographic characteristics included maternal age, race/ethnicity, pre-delivery body mass index (BMI). Obstetric characteristics included gestational age at the time of delivery, type of pregnancy (singleton vs. multiple gestation), and placenta previa. Perinatal factors included chorioamnionitis, the presence of labor or attempted induction prior to cesarean delivery, primary vs. repeat cesarean delivery, and neonatal birthweight. Race/ethnicity were categorized as follows: Caucasian, African-American, Hispanic, and Non-Hispanic Other. We constructed tertiles for neonatal birthweight: <3155g, 3155–3696g, >3696g.

Statistical Analysis

To estimate the comparative effectiveness of methylergonovine versus carboprost, a propensity-score based method was used. A propensity score was estimated using nonparsimonious multivariable logistic regression with all covariates included; methylergonovine exposure was selected as the dependent variable. Patients receiving carboprost were matched 1:1 on propensity score to patients receiving methylergonovine using a nearest neighbor algorithm with a caliper of 0.02 difference in propensity score. Matching was performed using the *psmatch2* command in STATA. If one or more variables remained unbalanced after matching, we performed further multiple logistic regression analyses by including interaction terms until the matched cohorts were balanced for all baseline covariates. Covariate balance was assessed by calculating the absolute standardized difference in proportions. Absolute standardized differences allow the assessment of balance on potential confounders before and after matching patients receiving methylergonovine to those receiving carboprost. An absolute standardized difference of 10% or more was considered to show covariate imbalance.²⁶

We calculated risk differences for the unmatched and matched cohorts. We calculated the relative risk (RR) and 95% confidence interval (CI) for hemorrhage-related morbidity for women receiving carboprost; women receiving methylergonovine were considered as the referent group.

Secondary Analyses

As previous studies have indicated that the risk of severe PPH is increased among women who experience spontaneous labor or labor induction prior to cesarean delivery,^{27, 28} we also repeated our analysis in a subgroup of women who underwent an induction of labor or who experienced spontaneous labor prior to cesarean delivery (n=840). Data analyses were performed using STATA version 12 (Stata Corp., College Station, TX).

RESULTS

Cohort Characteristics

In the Cesarean Registry, 57,182 women underwent cesarean delivery. After accounting for women who met the exclusion criteria, 1,335 women received a second line uterotonic: 870

women received methylergonovine and 465 women received carboprost (Figure 1). Within the cohort receiving a second line uterotonic, 157 (11.8%) women had hemorrhage-related morbidity (115 required postoperative transfusion; 44 required intraoperative transfusion; 29 required uterine artery ligation; 18 required hysterectomy related to uterine atony; and no patients received hypogastric artery ligation).

Compared to women who received methylergonovine, women who received carboprost were younger, more likely to be Hispanic and less likely to be Caucasian or African-American (Table 1). Women who received carboprost were more likely to be obese prior to delivery and were less likely to undergo preterm delivery. They also had higher rates of singleton pregnancy, chorioamnionitis, placenta previa, and labor or attempted induction. The rate of repeat cesarean delivery was slightly higher in women who received methylergonovine.

The propensity matching resulted in two cohorts of 369 women who received methylergonovine and carboprost respectively. The baseline characteristics in these two cohorts were well-balanced (Table 2). The standardized differences in the proportions for each covariate was <10% between women receiving methylergonovine compared to carboprost.

Association between Second Line Uterotonics and Hemorrhage-Related Morbidity

Hemorrhage-related morbidity was more common among women who received carboprost; 81 (17.4%) women in the carboprost group vs. 76 (8.8%) women in the methylergonovine group. Compared to women who received methylergonovine, those who received carboprost were at significantly higher risk of hemorrhage-related morbidity (unadjusted RR = 2.0; 95% CI = 1.5–2.7). After adjusting for confounders using propensity-score matching, the risk of hemorrhage-related morbidity remained increased for women who received carboprost (RR = 1.7; 95% CI = 1.2 – 2.6) (Table 3).

When we restricted our analysis only to women who underwent induction of labor or who experienced spontaneous labor, the risk of hemorrhage-related morbidity was higher among women who received carboprost (unadjusted RR=1.7; 95% CI=1.2 – 2.6), however the confidence interval for the risk estimate intersected with the null in the propensity-matched cohort (RR=1.6; 95% CI=0.9 – 2.8).

CONCLUSION

Using data from the prospectively collected MFMU Cesarean Registry, we examined a cohort of 1,335 women with uterine atony refractory to oxytocin who received either methylergonovine or carboprost. We found that women treated with methylergonovine were associated with reduced risk of hemorrhage-related morbidity compared with those treated with carboprost. To our knowledge, there are no data on the comparative effectiveness of methylergonovine and carboprost in the setting of PPH at cesarean delivery. Our finding of reduced hemorrhage-related morbidity associated with methylergonovine suggests that methylergonovine may be a more effective second line uterotonic. This finding has

important clinical relevance, especially in light of the increasing rate of atonic PPH after oxytocin use in many developed countries including the United States.²⁻⁵

There has been relatively limited data comparing the uterotonic efficacy of methylergonovine with carboprost. Several small randomized trials have compared the prophylactic effect of methylergonovine versus carboprost in the third stage of labor for the prevention of uterine atony. The results of these studies were mixed with some studies finding a reduction in blood loss with carboprost and others finding the opposite.¹²⁻¹⁵ Exactly what accounts for the heterogeneity in the results of these studies (such as differences in doses of uterotonics, patient characteristics or obstetric factors) is difficult to ascertain.

To the best of our knowledge, we are unaware of prior studies comparing the therapeutic efficacy of carboprost vs. methylergonovine for treating refractory uterine atony, the most common clinical indication for these agents. Furthermore, guidelines from the American College of Obstetricians and Gynecologists and other recognized obstetric bodies do not specifically indicate which second line uterotonic is preferred for treating uterine atony.^{9, 10, 24} Therefore, it is likely that practice patterns may vary among obstetricians in the use of second line uterotonics in this setting.¹¹ In our study cohort, there were nearly twice as many women who received methylergonovine compared to carboprost. These data suggest that physicians may have a baseline preference for methylergonovine as a second line uterotonic. This conclusion is supported by Bateman et al. who reported that the median hospital-level frequency of second line uterotonic use was higher for methylergonovine than carboprost (5.2% vs. 1.0%) among 2.1 million women hospitalized for delivery.¹¹

In our secondary analysis, the risk of morbidity was increased with carboprost compared with methylergonovine among women who underwent labor induction or who underwent spontaneous labor prior to cesarean delivery. However, the confidence interval intersected the null. Prior evidence indicates that oxytocin administration during labor may result in oxytocin receptor desensitization which can attenuate the oxytocin-mediated contractile response.^{29, 30} These findings have been substantiated clinically as oxytocin exposure during labor has been associated with an increased risk of severe atonic hemorrhage.³¹ Although it is possible that oxytocin receptor downregulation may mitigate the response of second line uterotonics acting through other receptors, Balki et al. demonstrated, in *an vitro* study using pregnant rat myometrium, that the uterotonic effects of Prostaglandin F2 alpha and ergonovine are unaffected by oxytocin desensitization.³² However, we are unaware of prospective clinical studies that support these *in vitro* findings.

Our study has several important strengths. We performed a secondary analysis using data derived from a multicenter, prospective registry.¹⁶ These data were manually abstracted from medical records by study staff at the time of discharge and were subject to strict quality control measures. The clinical detail of the data allows for the adjustment for important confounders that could impact the association between type of second line uterotonic administered and hemorrhage-related morbidity. We employed a robust statistical approach using propensity scores to account for these confounders in our analysis. Finally, the large observational dataset allowed us to address this important clinical question for which the

conduct of a prospective randomized clinical trial would be extremely challenging for several reasons including the low incidence and unpredictability in the timing of refractory uterine atony, and non-compliance of treatment allocation. To ethically conduct a randomized trial on this topic, patients would need to be enrolled prior to cesarean delivery. However, based on the data observed in our study, only 2% of patients (who met inclusion criteria) who underwent cesarean delivery required a second line uterotonic. Along with 24-hour availability of research personnel, a prohibitively large group of subjects would need to be enrolled. As a consequence, observational studies such as ours may therefore be the only viable study design to compare the effectiveness of these second line uterotonic agents for the treatment of refractory uterine atony.

Our study has to be considered in the light of certain limitations. The MFMU database does not include information on the severity of atony when second line uterotonics were administered. If physicians preferred carboprost over methylergonovine for treating severe atony then this might contribute to the association observed in our study. However, in the absence of data or guidelines to endorse this approach, this is an unlikely clinical scenario. Because the order of the administration of second line uterotonics could not be ascertained, we excluded patients who received both methylergonovine and carboprost. Since the failure of one uterotonic will frequently lead to the administration of a different uterotonic, exclusion of patients who received both medications would, if anything, bias the results of our comparative effectiveness analysis to the null. An additional limitation is the lack of information on the institutions or treating physicians, including training level of surgeon, institutional guidelines for the management of PPH, and institutional drug availability that did not allow us to account for institutions as a potential confounder. Additionally the dose of oxytocin and method of administration (bolus compared to infusion) utilized were not available in the database. Likewise, the database does not contain information on the use of other medications and interventions for treating refractory atonic PPH such as misoprostol; uterine compression sutures; hydrostatic balloon tamponade; pharmacological adjuncts, such as tranexamic acid; or interventional radiology.³³ These interventions may occur more commonly in current surgical practice than pelvic vessel ligation. However, these institutional factors and interventions would need to be differentially associated with carboprost or methylergonovine, which is unlikely from a clinical standpoint. As in all observational research, the results may be biased by unmeasured confounders, such as primary mode of anesthesia, magnesium sulfate use in non-hypertensive patients. Residual confounding may affect the magnitude of the association between carboprost and morbidity but would need to be very strong to fully explain the observed association. Lastly, data for the Cesarean Registry were collected between 1999 and 2002, therefore it is possible that obstetric and anesthesia practices for the management of refractory uterine atony may have changed over time. However, recent nationwide data from the United States suggest that methylergonovine and carboprost remain the most commonly used second line uterotonics for the treatment of uterine atony.¹¹ Furthermore, second line uterotonics, notably carboprost and methylergonovine, remain the most common treatment option for PPH before third line treatment is considered,³³ therefore our data remain relevant to contemporary obstetric practice.

In conclusion, we have examined the comparative effectiveness of these commonly used second line uterotonics in the setting of refractory atony during cesarean delivery. Our results suggest that methylergonovine is associated with reduced hemorrhage-related morbidity and therefore may be a more effective second line uterotonic agent compared to carboprost.

Acknowledgments

Financial Support: This study was supported and funded internally by the Department of Anesthesia and the Department of Obstetrics and Gynecology, Stanford University School of Medicine. A.J.B. is supported by an award from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (1K23HD070972). B.T.B. is supported by an award from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (K08HD075831).

We wish to acknowledge the assistance of the NICHD, the MFMU Network, and the Protocol Subcommittee in releasing the Cesarean Registry to investigators located at hospitals within the MFMU network. The contents of this report represent the views of the authors and do not represent the views of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network or the National Institutes of Health.

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Figure 1. Study Population

* 1 woman had missing data for asthma; 1 woman had missing data for chronic hypertension; 1 woman had missing data for uterine rupture or dehiscence. As more than one woman could have >1 condition/criteria for exclusion (asthma, chronic hypertension, hypertensive disorders or pregnancy, uterine rupture or dehiscence and abnormal placentation), the total number of women with these exclusion criteria is greater than 560.

Table 1

Baseline maternal, obstetric and perinatal characteristics of patients in entire cohort.

	Carboprost (n=465)	Methylergonovine (n=870)	ASD, %
Maternal Age:			
< 20 y	53 (11.4%)	89 (10.2%)	3.9
20 – 34 y	337 (72.5%)	585 (67.3%)	11.3
>34 y	75 (16.1%)	196 (22.5%)	–16.3
Race / Ethnicity:			
African-American	63 (13.5%)	195 (22.4%)	–23.3
Caucasian	132 (28.4%)	369 (42.4%)	–29.6
Hispanic	249 (53.6%)	249 (28.6%)	52.5
Other	21 (4.5%)	57 (6.6%)	–9.2
Pre-delivery BMI (kg/m ²):			
< 30	167 (35.9%)	365 (41.9%)	–12.3
30	254 (54.6%)	473 (54.4%)	0.4
Missing	44 (9.5%)	32 (3.7%)	
Gestational Age (weeks):			
< 37	70 (15.0%)	176 (20.2%)	–13.6
37	391 (84.1%)	693 (79.7%)	11.4
Missing	4 (0.9%)	1 (0.1%)	
Type of pregnancy:			
Singleton	438 (94.2%)	796 (91.5%)	10.5
Multiple	27 (5.8%)	74 (8.5%)	–10.5
Chorioamnionitis	108 (23.2%)	132 (15.2%)	20.4
Placenta Previa	23 (4.9%)	31 (3.7%)	5.9
Labor or Attempted Induction	310 (66.7%)	530 (60.9%)	12.1
Type of Cesarean Delivery:			
Primary	271 (58.3%)	506 (58.2%)	2.0
Repeat	185 (39.6%)	361 (41.5%)	–3.8
Missing	10 (2.1%)	3 (0.3%)	
Neonatal Birthweight Tertiles (g):			
< 3155	127 (27.3%)	318 (36.5%)	–19.8
3155 – 3696	151 (32.5%)	294 (33.8%)	–2.8
> 3696	187 (40.2%)	258 (29.7%)	22.2

Data presented as n (%)

ASD = Absolute standardized difference; BMI = Body Mass Index

Table 2

Baseline maternal, obstetric and perinatal characteristics of patients in propensity-matched cohort.

	Carboprost (n=369)	Methylergonovine (n=369)	ASD, %
Maternal Age:			
< 20 y	42 (11.4%)	37 (10.0%)	4.4
20 – 34 y	263 (71.3%)	267 (72.4%)	–2.4
> 34 y	64 (17.3%)	65 (17.6%)	–0.7
Race / Ethnicity:			
African-American	54 (14.6%)	49 (13.3%)	3.9
Caucasian	125 (33.9%)	130 (35.2%)	–2.8
Hispanic	169 (45.8%)	167 (45.3%)	1.1
Other	21 (5.7%)	23 (6.2%)	–2.3
Pre-delivery BMI (kg/m ²):			
< 30	152 (41.2%)	146 (39.6%)	3.3
30	217 (58.8%)	223 (60.4%)	–3.3
Gestational Age (weeks):			
< 37	57 (15.5%)	61 (16.5%)	–3.0
37	312 (84.5%)	308 (83.5%)	3.0
Type of pregnancy:			
Singleton	18 (4.9%)	15 (4.1%)	3.9
Multiple	351 (95.1%)	354 (95.9%)	–3.9
Chorioamnionitis	78 (21.1%)	71 (19.2%)	4.7
Placenta Previa	16 (4.3%)	20 (5.4%)	–5.0
Labor or Attempted Induction	238 (64.5%)	234 (63.4%)	2.3
Type of Cesarean Delivery:			
Primary	216 (58.5%)	214 (58%)	1.1
Repeat	153 (41.5%)	155 (42%)	–1.1
Neonatal Birthweight Tertiles (g):			
< 3155	104 (28.2%)	110 (29.8%)	–3.6
3155 – 3696	127 (34.4%)	123 (33.3%)	2.3
> 3696	138 (37.4%)	136 (36.9%)	1.1

Data presented as n (%)

ASD = Absolute standardized difference; BMI = Body Mass Index

Table 3

Risk of hemorrhage-related morbidity in women receiving carboprost as compared to women receiving methylergonovine.

	Carboprost n (%)	Methylergonovine n (%)	Relative Risk* (95% CI)
Hemorrhage-related morbidity:			
Unadjusted	81 / 465 (17.4%)	76 / 870 (8.7%)	2.0 (1.5 – 2.7)
Propensity score matched	59 / 369 (16.0%)	34 / 369 (9.2%)	1.7 (1.2 – 2.6)
Sensitivity Analysis:			
Women who underwent IOL or spontaneous labor			
Unadjusted	46 / 310 (14.8%)	45 / 530 (8.5%)	1.7 (1.2 – 2.6)
Propensity score matched	31 / 237 (13.1%)	19 / 237 (8%)	1.6 (0.9 – 2.8)

* Reference group = women who received methylergonovine

IOL = Induction of labor