ORIGINAL ARTICLE

Outcomes after institution of a new oxytocin infusion protocol during the third stage of labor and immediate postpartum period

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ABSTRACT

Background: Due to safety concerns when oxytocin is administered in an uncontrolled fashion, and recent dose–response data that indicate oxytocin’s effectiveness at doses lower than those traditionally used, we instituted a new protocol for the infusion of oxytocin during the third stage of labor and in the immediate postpartum period. We undertook this study to confirm that this change in practice did not have untoward effects on postpartum hemorrhage rates.

Methods: In this retrospective review, patients who delivered in the six months before (PRE group) and patients who delivered in the six months after (POST group) the new protocol had been introduced were identified through an institutional database and their medical records were reviewed. The primary outcome variable was the postpartum hemorrhage rate. Secondary outcomes included maternal and fetal co-morbidities, protocol compliance, administration of other uterotonic agents, use of Bakri balloons and B-Lynch sutures, rate of uterine artery embolization and peripartum hysterectomy, need for red blood cell transfusion, and drop in hemoglobin after delivery. Categorical data were analyzed using Chi-squared or Fisher’s Exact test, as appropriate. Continuous data were analyzed using a Mann-Whitney U test. A P value <0.05 was required to reject the null hypothesis.

Results: A total of 1572 medical records were reviewed. Postpartum hemorrhage occurred in 9.0% of PRE patients and 7.1% of POST patients, and was not different between groups (P = 0.17). Carboprost use was lower in the POST group, but no other differences were noted.

Conclusion: Adoption of a protocol to infuse oxytocin in a controlled manner at a lower dose than that historically used was not associated with an increased incidence of postpartum hemorrhage.

Keywords: Obstetrics; Obstetric anesthesia; Postpartum hemorrhage; Medication safety; Oxytocin

Introduction

The American College of Obstetricians and Gynecologists (ACOG), along with other experts, recommends the administration of uterotonic agents during the third stage of labor and immediate postpartum period to prevent uterine atony and accompanying hemorrhage.1–3 Unfortunately, oxytocin can be associated with serious side effects including tachycardia, hypotension, myocardial ischemia, and even death, especially in hypovolemic or other hemodynamically-compromised women.4–8 Many of these adverse effects follow dose–response kinetics.9,10 The dose of oxytocin required to produce uterine contractions postpartum is much lower than previously thought.11–13 In addition, bolus dosing of oxytocin followed by infusion is not more effective than intravenous infusion alone, and is no longer recommended.14

Based on the increased awareness of the dangers of administration of high-dose oxytocin, and these dose–response data, experts have advised practitioners to devise rational, evidence-based protocols governing the use of oxytocin during the third stage of labor and postpartum period.15,16 However, no clear guidelines exist, and many clinicians are hesitant to adopt new strategies because of concerns for adverse outcomes, in particular, postpartum hemorrhage (PPH). We instituted an evidence-based protocol for the controlled administration of oxytocin after delivery of the neonate. We then undertook a chart review to determine compliance with the new approach, and examine adverse outcomes related to PPH in order to allay clinicians’ fears regarding the effects of such efforts on postpartum bleeding. To the authors’ knowledge this is the first such report to
appear in the literature, and should give practitioners confidence in the use of these recommended protocols.

Methods

This study was approved by the University of Chicago Institutional Review Board. All patients who delivered at the University of Chicago Women’s Care Center were identified through a University-maintained quality assurance perinatal database and separated into two groups. The first, or pre-protocol, group (PRE) consisted of parturients who delivered during the time period from 1 August 2010 through 31 January 2011. The second, or post-protocol, group (POST) consisted of those who delivered between 1 March 2011 and 31 August 2011. The period from 1 February through 28 February 2011 was omitted as the protocol was introduced during this time and full compliance could not be assured.

PRE group patients received oxytocin immediately following delivery of the neonate via the conventional practice at our institution, i.e., 10–40 IU of oxytocin in 1 L of crystalloid administered at an unspecified and uncontrolled rate. Oxytocin was not administered via bolus. In the event of suspected uterine atony, additional uterotonic medications, including more oxytocin, could be used at any time. The choice of which uterotonic medication to use was left to the attending physician. With appropriate education the new protocol was introduced in the month between the PRE and POST periods. POST patients received oxytocin according to our new evidence-based protocol (Appendix A). Oxytocin was administered at a rate of 0.3 IU/min (18 IU/h) for the first hour with the option of increasing the rate to 0.6 IU/min (36 IU/h) in the event of uterine atony. If atony persisted, additional uterotonic medications could be administered at the physician’s discretion. If bleeding remained stable, after a 1-h period the oxytocin infusion rate was decreased to 0.06 IU/min (3.6 IU/h) until the patient was discharged from the labor and delivery suite.

Data were extracted from the quality assurance perinatal database regarding obstetric conditions and management, and maternal and fetal co-morbidities that may be associated with PPH,17 including induction of labor, administration of oxytocin during labor for either induction and/or augmentation, instrumental vaginal delivery (forceps or vacuum), trial of labor after cesarean (whether successful or unsuccessful), presence of multiple gestation, polyhydramnios (amniotic fluid index >25 cm), preterm/prematurity (before 37 weeks estimated gestational age and before onset of contractions) rupture of membranes, hypertensive diseases of pregnancy (chronic hypertension, preeclampsia, eclampsia, and/or gestational hypertension), diabetes, placental abruption, placenta previa, chorioamnionitis (clinical diagnosis), neonatal weight >4000 g, intrauterine fetal demise (occurring after 20 weeks estimated gestational age), 3rd or 4th degree laceration, placenta removed via dilation and curettage procedure, and no or late (after 24 weeks estimated gestational age) prenatal care.

Medical records of identified women were examined. Note was made of mode of delivery, compliance with the new protocol, and rates of PPH, defined as >500 mL estimated blood loss after vaginal delivery, or >1000 mL after cesarean delivery. Data were also extracted regarding use of any uterotonic medications other than oxytocin, use of Bakri balloons, use of B-Lynch sutures, rate of uterine artery embolization, rate of peripartum hysterectomy, and the need for red blood cell (RBC) transfusion. Pre- (at time of admission to labor and delivery unit) and post- (most often postpartum day 1) delivery hemoglobin concentrations were recorded. Difference in hemoglobin was defined as pre-delivery hemoglobin minus post-delivery hemoglobin.

Statistical analysis

Our institutional Quality Committee charged us with monitoring PPH data six months after the introduction of the protocol. Power analysis was therefore based on a sample size of approximately 800 patients per group (6-month sample each group, institutional data), baseline rate of PPH of 8% (institutional data), and α = 0.05, and demonstrated 76% power to determine an effect size of 0.5 (i.e., an increase in the rate of PPH to 12%). Categorical data were analyzed using Chi square or Fisher’s Exact test, as appropriate. Continuous data were tested for normality and non-parametric data were analyzed using a Mann-Whitney U test. A P value <0.05 was required to reject the null hypothesis.

Results

There were 800 women in the PRE group with 549 vaginal deliveries and 251 cesarean deliveries. The POST group had 772 women with 572 vaginal deliveries and 200 cesarean deliveries. Chart review demonstrated 99.4% compliance with the new protocol. Women in the PRE group were more likely to be hypertensive and more likely to have obtained no or late prenatal care as compared to the POST group. No other obstetric or co-morbidity differences existed between groups (Table 1).

The overall PPH rate for the PRE and POST groups was 9.0% vs. 7.1% (P = 0.17), respectively (Table 2). Carboprost was used at a lower rate in the POST patients (Table 3). There were no differences between the PRE and POST groups in any of the other indicators of PPH, including administration of other individual uterotonic agents, or the use of any uterotonic agent other than oxytocin. Similarly, use of Bakri balloons, B-Lynch sutures, uterine artery embolization, and hysterectomy were not different; nor was the need for RBC transfusion. The median difference in hemoglobin was 1.6 g/dL in the
PRE group and 1.1 g/dL in the POST group; these decreases were not different \((P = 0.5)\) (Fig. 1).

**Discussion**

Our results demonstrate that adoption of an evidence-based oxytocin infusion protocol for the third stage of labor and immediate postpartum period is feasible, as demonstrated by our 99.4% compliance rate. In addition, use of such a protocol did not increase the risk of PPH over the study period.

ACOG defines PPH as an estimated blood loss of >500 mL after a vaginal delivery or >1000 mL after a cesarean delivery.\(^1\) PPH remains a leading cause of maternal mortality, responsible for 12% of USA pregnancy-related deaths,\(^1\) and its incidence appears to be increasing.\(^1\) ACOG recommends active management of the third stage of labor, including prophylactic administration of uterotonics agents, to prevent uterine atony, the most common cause of PPH.\(^1\)

Active management, specifically oxytocin administration, decreases blood loss and rates of PPH and transfusion.
compared to expectant management. However, oxytocin has a narrow therapeutic range, and can be associated with serious side effects including hypotension and tachycardia. These perturbations may be accompanied by chest pain, ST-segment changes, and transient myocardial ischemia, possibly secondary to coronary vaso- spasm. Hypovolemic women, or those with cardiovascular pathology, including severe preeclampsia, may be less able to tolerate these effects, and oxytocin-related deaths in the setting of hypovolemia have been reported. Excessive doses of oxytocin given concomitantly with large volumes of intravenous fluids, especially those containing free water, can lead to severe hyponatremia, seizures, and coma, due to oxytocin’s structural similarity to vasopressin.

Knowledge of both the dangers associated with rapid oxytocin administration and the dose–response range of the drug have recently been called into question. Conventional USA practice is to place 10–40 IU of oxytocin in a 1-L bag of crystalloid and administer it at an unspecified and uncontrolled infusion rate, usually “wide open” and not through an infusion pump. In the event of uterine atony, the infusion rate is often increased to the point where doses are close to those achieved with bolus administration, a practice advised against by experts. The Joint Commission points out the dangers of this type of uncontrolled administration of any potentially dangerous drug. Consequently, some authors have recommended that practitioners adopt protocols more consistent with safe administration of oxytocin. We therefore devised a protocol compliant with Joint Commission expectations, based on currently available dose–response data. Due to the paucity of guidelines, the protocol was necessarily somewhat subjectively designed, but is literature-based, and consistent with expert recommendations.

The ED$_{90}$ of bolus-dose oxytocin for adequate uterine contractions is 0.35 IU in non-laboring women undergoing cesarean delivery, and approximately 3 IU in laboring women having cesarean delivery. However, a recent study demonstrated that administering a 5 IU bolus of oxytocin before an infusion does not alter the need for additional uterotonic drugs in the first 24 h, estimated blood loss, or transfusion requirements as compared to using an infusion without an initial bolus dose. Although the study was not powered to detect differences in side effects between the two groups, there was a trend toward less hypotension in the infusion-only group. Other investigators have demonstrated more tachycardia and hypotension in patients receiving an oxytocin bolus compared to infusion. The ED$_{90}$ of oxytocin administered via infusion without bolus in non-laboring women is approximately 0.3 IU/min. Based on the evidence, our protocol calls for the initial administration of 0.3 IU/min (18 IU/h) of oxytocin without bolus dosing during the third stage of labor. Limited data exist regarding oxytocin infusion rate in the setting of uterine atony, and so we chose to allow for the administration of twice the ED$_{90}$ (0.6 IU/min, or 36 IU/h) when atony occurred.

Our protocol was written with input from the obstetric, maternal fetal medicine, anesthesiology, and nursing departments. It was introduced with extensive education via electronic communication, written communication, and educational in-service, and all practitioners were expected to adhere to it. All forms of oxytocin other than the 30 IU/500 mL preparation were removed from the Labor and Delivery Unit, further encouraging use of the protocol-specified solution. Cooperation with the new protocol was excellent, as evidenced by the 99.4% compliance rate in the POST period. Many clinicians are hesitant to adopt these strategies, which employ a much lower dose of oxytocin than traditionally used in the USA, because of concerns for increased rates of PPH. The care-givers on our labor and delivery unit shared these concerns, and this chart review was undertaken as a quality improvement project, in order to ensure that PPH rates were not adversely affected after the protocol-driven change in practice.

The proportion of PPH in this study (9% PRE and 7.1% POST) is higher than the approximately 3% reported elsewhere. Our institution serves a high-risk inner city patient population and also functions as a tertiary care center for high-risk pregnancies. Several of the conditions listed in Table 1 occurred at higher rates in our population than reported nationally, or occurred at the upper limits of the reported range, including induction of labor (29.4% in our study vs. 19.4% nationally), preterm/premature rupture of membranes (22.9% vs. 3%), hypertensive diseases of pregnancy (20.1% vs. 8%), diabetes (6.9% vs. 2.8–5.4%), placental abruption (1.5% vs. 1%), placenta previa (0.7% vs. 0.4%), chorioamnionitis (4.8% vs. 1–4%), and intra-

![Fig. 1 Difference in hemoglobin. Box plots of difference in hemoglobin (calculated as hemoglobin concentration before delivery – hemoglobin concentration after delivery). The box represents the 25th to 75th percentile, the line within the box is the median, and the asterisks represent outliers.](Image)
uterine fetal demise (3.9% vs. 0.67–0.9%). In light of this, the elevated PPH rate is not surprising. It is particularly relevant that the new dosing protocol, which calls for lower doses of oxytocin than traditionally used in the USA, did not increase PPH in this at-risk population.

It is unclear why the use of carboprost dropped after protocol initiation. This may reflect a subtle positive impact on PPH rates, although rate of use of any uterotonic agent did not change. Alternatively, unaccounted for factors may have influenced this finding, or it may represent a spurious result.

There are several limitations to our study. The first is that we did not record the incidence of adverse side effects such as hypotension, tachycardia, chest pain, or myocardial ischemia. Not only was that not an objective of this study, we also felt that side-effect data would be unreliable in a retrospective chart review. As our protocol mandates lower doses of oxytocin than those previously used, we anticipated that the incidence of such adverse events would be lower. Another limitation lies in the potential inaccuracy of estimated blood loss. It is standard procedure at our institution to estimate blood loss visually, and to weigh absorbent pads and sponges any time blood loss is judged to exceed 500 mL after vaginal delivery, or 1000 mL after cesarean delivery. This would seem to indicate that those patients defined as having PPH did indeed meet the diagnostic criteria. However, as visual estimation of blood loss is inaccurate, this may have affected our results.

An additional limitation is related to the higher rates of hypertensive diseases of pregnancy and no or late prenatal care that occurred in the PRE versus the POST population. The explanation for this disproportion remains unclear. If hypertensive diseases of pregnancy and late provision of prenatal care increase risk of PPH, then this imbalance could theoretically have biased the results in favor of the POST group. It seems unlikely, however, that this small decrease in co-morbidities explains our results entirely.

In summary, infusing oxytocin according to an evidence-based protocol did not increase the incidence of PPH in our high-risk patient population.

Disclosure
The authors received no external financial support and have no conflicts of interest to declare.

References


Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijoa.2013.03.007.