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Higher-Dose Oxytocin and Hemorrhage After Vaginal Delivery: A Randomized Controlled Trial

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Abstract

Objective—Higher-dose oxytocin is more effective than lower-dose regimens to prevent postpartum hemorrhage following cesarean delivery. We compared two higher-dose regimens (80U and 40U) to our routine regimen (10U) among women who delivered vaginally.

Methods—In a double-masked randomized trial, oxytocin (80U, 40U or 10U) in 500ml was given over 1 hour after placental delivery. The primary outcome was a composite: any treatment of uterine atony or hemorrhage. Prespecified secondary outcomes included outcomes in the primary composite and a decline of 6% or greater in hematocrit. A sample size of 600 per group (N=1800) was required to compare each of the 80U and 40U to the 10U group. At planned interim review (n=1201), enrollment in the 40U group was stopped for futility and enrollment continued in the other groups.

Results—Of 2,869 women, 1,798 were randomized: 658 to 80U, 481 to 40U and 659 to 10U. Most characteristics were similar across groups. The risk of the primary outcome in the 80U group (6%; RR 0.93, 95% CI: 0.62–1.40) or the 40U group (6%; 0.94, 0.61–1.47) was not different compared with the 10U group (7%). Treatment with additional oxytocin after the first hour was less frequent with 80U compared with 10U (RR 0.41; 0.19–0.88) as was a 6% or greater decline in hematocrit (0.83; 0.69–0.99); both outcomes declined with increasing oxytocin dose. Outcomes were similar between the 40U and 10U groups.

Conclusion—Compared with 10 units, 80 or 40 units of prophylactic oxytocin did not reduce overall postpartum hemorrhage treatment when given in 500ml over 1 hour for vaginal delivery. Eighty units decreased the need for additional oxytocin and the risk of a 6% or greater decline in hematocrit.

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Introduction

Obstetric hemorrhage is the leading cause of maternal death worldwide and is among the top three causes of these deaths in the US.¹⁻² Postpartum hemorrhage is the most common type of obstetric hemorrhage, and uterine atony accounts for over 80% of postpartum hemorrhage.³ Prophylactic use of uterotonic agents prevents uterine atony and reduces the risk of postpartum hemorrhage by 40–50%.⁴⁻⁷ Compared with methylergometrine and misoprostol, oxytocin has a good safety profile and induces fewer, if any, side effects.^{6,8-9} In the United States, oxytocin is the uterotonic routinely used for prophylaxis. In spite of its widespread use, the optimal prophylactic oxytocin dose-regimen is unknown. Twenty units of oxytocin given in 1 liter of crystalloid solution “at a rate of 10 ml/minute for a few minutes to get an adequate uterine tone, then reduced to 1–2 ml per minute during postpartum recovery in the delivery suite and then discontinued prior to transfer to the postpartum suite” is a commonly recommended dose-regimen.¹⁰ The dose-regimen corresponds to that routinely used after vaginal delivery at our institution: 10 units of oxytocin in 500cc of crystalloid solution given over 1 hour. For cesarean delivery, a higher dose-regimen (80 units oxytocin in 500 cc of crystalloid) is used at our institution based on positive findings from a randomized trial that included 321 women who underwent cesarean delivery.¹¹ In that study, compared with women who received the higher dose regimen, the standard dose (10U/500cc) was associated with a two-fold increase in the risk of uterine atony or postpartum hemorrhage requiring treatment with uterotonics (including additional oxytocin) and nearly a 5-fold increase in the need for second-line uterotonics such as methergine and hemabate.¹¹ Although vaginal deliveries account for over two-thirds of all births,¹² it remains unknown whether a higher dose of prophylactic oxytocin is similarly more effective among women delivered vaginally. If this were so, we could have a single dedicated oxytocin dose concentration to prevent postpartum hemorrhage. Therefore, we compared the effectiveness of two higher dose prophylactic oxytocin regimens to the standard dose regimen for vaginal deliveries. We hypothesized that higher doses of oxytocin (80 units or 40 units) as compared with the standard 10 unit dose would safely reduce uterine atony or postpartum hemorrhage requiring treatment.

Methods and Materials

We conducted a single center double-blind randomized controlled trial that included women with viable pregnancies undergoing vaginal delivery at 24 weeks of gestation or greater at University Hospital, Birmingham, AL. Those who underwent cesarean delivery or who had a fetal demise, a diagnosis of coagulopathy, pulmonary edema or cardiomyopathy were excluded. Eligible women were approached and consented at the time of admission for delivery (spontaneous labor or induction). The Institutional Review Board of the University of Alabama at Birmingham approved the study.

Study interventions, allocation and blinding

Women were randomized to one of the three study arms according to a confidential computer-generated block randomization algorithm. The algorithm randomly allocated 3 women to each study dose in blocks of size 9, thus ensuring equal allocation among the study arms. The randomization scheme was sequentially numbered and delivered to the pharmacy. The investigational drug pharmacists prepared identical oxytocin bags by adding 10U, 40U or 80U of oxytocin into a malleable bag of 500ml of normal saline. The bags were prepared in advance of patient randomization, were numbered according to the randomization scheme provided, and were stored at room temperature in a dedicated and secure research study closet on Labor and Delivery. Only the investigational pharmacist and one statistician, who had no role in patient enrollment or outcome ascertainment, had knowledge of the code matching the sequential number to oxytocin dose or the size of the

randomized blocks. At the time of vaginal delivery of each consented patient, the next sequentially numbered oxytocin bag was dispensed to the nurse. The sequential drug number together with the patient's name and medical record number were entered into the randomization log. At this point the patient was considered randomized. Upon delivery of the placenta, the study medication bag was then administered to the patient over 1 hour using an infusion pump for precision. During this hour, use of additional oxytocin to treat uterine atony or hemorrhage was avoided (second line uterotonics such as hemabate or methergine were used). However, additional oxytocin could be utilized for treatment after completion of the prophylactic infusion (i.e. after 1 hour).

Outcomes and definition

The primary outcome was a composite outcome of uterine atony or hemorrhage requiring treatment including treatment with any uterotonic, uterine tamponade (typically with a Bakri balloon), interventional radiology for uterine or other arterial embolization, surgery or blood transfusion. Key prespecified secondary outcomes included individual outcomes in the primary composite, a 6% unit or greater decline in hematocrit after delivery, clinically estimated blood loss, endometritis, hospital stay and safety outcomes (need for fluid bolus, vasopressor treatment and fluid overload requiring diuretic therapy). Need to treat uterine atony or postpartum hemorrhage with uterotonics is recommended as a priority outcome measure for postpartum hemorrhage by a World Health Organization international panel.¹³ At our institution, the protocol for postpartum hemorrhage requires routine application of fundal massage after delivery; bimanual palpation is used if there is uterine atony or ongoing hemorrhage. The absolute decline in hematocrit was calculated by subtracting the first postpartum hematocrit (typically collected within 8 to 24 hours) from the most recent pre-delivery hematocrit (typically drawn at the time of admission for delivery). A 6% unit decline in hematocrit (e.g. 35% to 29%) was chosen since it corresponds on average to a 2 unit blood loss which we consider to be clinically significant in the context of a vaginal birth). Need for blood transfusion was based on actual administration of whole or packed red blood cells prior to discharge. The need for fluid bolus and need for pressor treatment were as determined and ordered by the obstetric or anesthetic provider. Endometritis was based on a clinical diagnosis by the obstetric providers and the use of antibiotics for treatment. All outcomes were ascertained by chart abstraction until discharge from hospital by trained research nurses.

Sample Size and Statistical Analyses

Two separate primary oxytocin dose comparisons were specified: 80U vs. 10U and 40U vs. 10U. As a secondary comparison we planned to evaluate for trend in outcomes across 10, 40 and 80U dose-groups. For both primary pair-wise comparisons, we estimated a sample size of 600 per group, or a total of 1800, based on an assumed primary outcome rate of 18% in the 10U group, alpha of 0.05 for each comparison, 80% power and a hypothesized 33% reduction in the primary outcome (i.e. 18% to 12% for 80U vs 10U and 18% to 12% for 40U vs 10U). The baseline rate of 18% in the 10U group was estimated from a review of outcomes among vaginal deliveries conducted over a month at our institution. A single interim analysis was planned at enrollment of 1200 women, approximately two-thirds of the total planned sample size. The Lan-DeMets spending function approximation to O'Brien-Fleming stopping boundaries¹⁴ was used to adjust the level of significance of each primary analysis at both the interim review (significance level = 0.017) and at study termination (significance level = 0.033) to preserve the overall 0.05 level of significance. At the planned interim review (n=1201 randomized) by the data safety and monitoring board, boundaries for early termination were not exceeded. An investigation for futility concluded that the conditional power for the 40U vs. 10U comparison was <1%. The 40U arm was thus

stopped for futility and enrollment was continued in the 10U and 80U dose arms to the original total sample size of 1800.

Analyses were by intent-to-treat. Baseline characteristics including risk factors for postpartum hemorrhage^{15–16} and outcomes were compared between groups. Chi-square, ANOVA, and Kruskal-Wallis tests were used as applicable for baseline and outcome comparisons among the 3 treatment groups. Chi-square tests and ANOVA, were used for two group tests. Fisher's exact and Wilcoxon rank-sum tests were used where appropriate. We computed relative risks and 95% confidence intervals for pairwise comparisons of outcomes. Tests for trends in dichotomous outcomes across groups were based on the Mantel Haenszel test and tests for ordered differences in quantitative measures were based on the nonparametric Jonckheere-Terpstra test¹⁷. All statistical tests, with the exception of the primary outcome as previously described, were evaluated at a 0.05 level of significance. SAS software (version 9.2; SAS Institute Inc, Cary, NC) was used for all statistical analyses. The trial was approved by our institutional IRB.

Results

From November 2008 through June 2010, 2,869 women were screened and 1,798 randomized: 658 to 80 units of prophylactic oxytocin, 481 to the 40U group (discontinued) and 659 to the 10U group (Figure 1). The baseline characteristics of women were similar except the incidence of chorioamnionitis was higher, and the frequency of spontaneous membrane rupture and prolonged second stage of labor was lower in the 10U group (Table 1).

Overall, the primary composite outcome of treatment for hemorrhage or atony occurred in 6–7% of the study sample. Compared to the 10U group, higher doses of oxytocin did not significantly decrease the unadjusted risk of the primary outcome; there was no linear dose-response trend across groups (Table 2). Higher doses of oxytocin did not decrease treatment of uterine atony or obstetric hemorrhage with any uterotonics. However, 80 units but not 40 units of oxytocin compared to 10 units significantly decreased the need for treatment with additional oxytocin – corresponding to a decreased need for treatment after the first hour or on the postpartum suite. There was also a significant decreasing trend in the need for treatment with oxytocin (3% to 2% to 1%) with increasing dose of prophylactic oxytocin. All other components of the primary outcome including the rare need for tamponade, surgery, interventional treatment or blood transfusion did not differ by dose of prophylactic oxytocin.

Mean change in hematocrit following delivery was not significantly different between groups. However, fewer women in the 80U group, but not in the 40U group, compared to the 10U group had a 6% or greater decline in hematocrit (Table 3). The incidence of this clinically important decline in hematocrit decreased modestly but significantly from 28% to 23% as prophylactic oxytocin dose increased from 10 units to 80 units ($p < 0.05$). Other secondary outcomes including estimated blood loss (mean and clinically estimated blood loss > 500 ml), fluid bolus or pressor treatment for hypotension, fluid overload, endometritis and prolonged hospitalization (4 or more days) did not differ by dose of prophylactic oxytocin. Since need for fluid bolus or pressor treatment in labor was primarily the result of epidural, we restricted the study population to women who did not receive an epidural: the incidence of fluid bolus by decreasing dose of oxytocin was 0%, 0% and 0.3% (p -value for trend > 0.999). Results for pressor treatment were identical.

Relative risks (95% CI) for the relationship between key study outcomes and higher doses of oxytocin compared to the 10 unit dose are given (Table 4). There were no significant

differences between higher doses (80 or 40 units) and the 10 unit standard dose oxytocin for the primary composite outcome or need for any uterotonic to treat postpartum hemorrhage. However, there was a reduction in the need for oxytocin to treat uterine atony or postpartum hemorrhage, primarily on the postpartum floor in the post-recovery period. Results for a 6% or greater decline in hematocrit suggested a lower incidence with 80 units but not with 40 units compared with 10 units of oxytocin (Table 4).

We conducted additional (post-hoc) analyses to further evaluate our findings. The mean times ($\pm$ sd) between pre- and post-delivery hematocrit revealed no differences by group: 25.0 ± 11.3 , 25.2 ± 12.1 and 25.3 ± 11.5 hours respectively for 10, 40 and 80U groups; p -value = 0.891. The respective mean times ($\pm$ sd) from delivery to post-delivery hematocrit were also similar: 15.5 ± 8.0 , 16.3 ± 9.0 and 16.0 ± 8.8 ; p -value = 0.351. We compared the incidence of hematocrit decline greater than the pre-specified 6% cut-off: 80U compared with 10U of prophylactic oxytocin was associated with a lower incidence of an 8% or greater decline in hematocrit (9% vs. 13%; $p = 0.013$) but not with a 10% or greater decline (4% vs. 5%; $p = 0.301$). Finally, results of analyses adjusting for the differences in were consistent with our main findings.

Discussion

Overall, higher doses of prophylactic oxytocin (80U or 40U), as compared with the standard dose of 10 units of oxytocin when given in 500ml of crystalloid over one hour following vaginal delivery, did not significantly reduce the incidence of the primary composite outcome of uterine atony or hemorrhage requiring any treatment. However, 80U of oxytocin reduced the frequency of 2 pre-specified secondary outcomes: hemorrhage requiring treatment after the 1st postpartum hour and a decline in hematocrit greater than 6% units. There was a significant dose-response trend in these outcomes (reducing incidence with increasing dose of prophylactic oxytocin). Additionally, higher dose regimens were not associated with an increase in adverse events such as hypotension or fluid overload.

Findings from the few available studies examining various outcomes in relation to dose-regimens suggest that both dose and rate of administration (including intravenous bolus) play a role.^{11,18–20} Typically, these studies have associated higher doses of prophylactic oxytocin with beneficial impact on outcomes such as estimated blood loss, decline in hematocrit or need for additional uterotonics among women who underwent cesarean delivery.^{11,18–20} In two studies, women undergoing scheduled cesarean received a 5 unit IV bolus versus 35 units (5 unit bolus+30 units over 4 hours) of prophylactic oxytocin.^{18,20} Women in the higher dose group had significantly lower mean estimated blood loss and lower frequencies of blood loss greater than 500ml or greater than 1000 ml, need for uterotonic treatment or blood transfusion.^{18,20} In another small study of cesareans, higher dose of oxytocin was associated with a higher uterine tone and a non-significant reduction in need for additional uterotonic.¹⁹ Finally, in the previous trial at our institution 80 units as compared with 10 units of prophylactic oxytocin reduced the need for any uterotonic treatment as well as the need for treatment with second line agents among women who underwent cesarean delivery after labor.¹¹ Our current study is one of the largest randomized trials comparing different doses of oxytocin to prevent postpartum hemorrhage but focuses on women who underwent vaginal delivery. While contrary to the prior study we did not observe a significant reduction in need for any uterotonic treatment, the findings for pre-specified secondary outcomes (hematocrit decline ≥ 6 units and need for oxytocin after the 1st hour) do suggest potential benefits of higher dose regimens among women following a vaginal birth. Randomization provides balance across groups for baseline hematocrit and times to post-delivery hematocrit (a proxy for hydration during labor). Indeed considering labor hydration, the amount of blood loss needed for a 6 unit drop in hematocrit may be

higher than the postulated 2 units. Support for the safety of higher doses of oxytocin is evident from prior studies including those of concentrated oxytocin protocols for mid-trimester pregnancy termination or induction of delivery^{11, 21–22}; these regimens have been generally reported to be safe.

The discrepancy in primary outcome results could be attributed at least in part to differences in the risk profile of the study population and the higher rate of infusion of prophylactic dose regimens in the previous study (500cc given over half an hour for cesareans vs. over 1 hour for vaginal delivery in our study).¹¹ The discrepancy may also be the consequence of our study's limited power to discern differences in the primary outcome. Our original estimated sample size was based on an 18% incidence of the primary outcome in the low dose group. This included use of additional oxytocin to treat atony occurring while the prophylactic infusion was ongoing. However, based on pharmacy recommendations, we did not give additional oxytocin during the first hour (concurrent with the prophylactic infusion). Instead, second line uterotonics were given if treatment was indicated in the first hour. The smaller than expected incidence of uterotonic treatment likely reflects a higher threshold to use methergine or prostaglandins as first-line treatment for hemorrhage or atony. The outcome rate of 7% would have required approximately double our current sample size to be able to detect a 33% reduction in the incidence of the primary composite outcome. At interim review, considering the 80% reduction in need for 2nd line agents to treat from a baseline of 9% in the prior trial and the futility of the intermediate study dose for the primary outcome, we opted to continue the enrollment in the 2 remaining arms to the original total sample size. We estimated that the sample size cumulated in these 2 groups would provide 80% power to detect a 50% reduction in the primary outcome from the new baseline of 7%. Apart from power considerations, our study had other limitations. Given the inherent difficulty in validly estimating postpartum blood loss, we used clinical outcomes as a proxy for blood loss. In our protocol oxytocin was given only after placental delivery. Although timing of administration does not appear to make a difference,^{23–24} we cannot guarantee that our results with higher doses would be the same if we initiated prophylactic oxytocin prior to placental delivery.

Overall, higher doses of prophylactic oxytocin appear to be beneficial in preventing measures of postpartum hemorrhage among women delivered by cesarean.^{11,18–20} Therefore, doses as high as 80 units given over 30 minutes are used for cesareans. However, in our study of women undergoing vaginal delivery, the incidence of uterine atony requiring treatment was not significantly reduced when 80 units were given over 1 hour, although we observed a reduction in the need for oxytocin in the postpartum suite as well as a reduction in a drop in hematocrit above 6 units with higher dose oxytocin. Based on the negative findings concerning our primary outcome, practitioners may opt not to use a high dose of oxytocin following vaginal delivery. Alternatively, others may choose to use 80 units considering the potential for benefits based on the positive findings for secondary outcomes. This is particularly applicable in settings where the high dose is already being used for cesarean deliveries. This would enhance efficiency by allowing for a single pre-mixed oxytocin dose bag for prophylaxis (as opposed to one for cesareans and another for vaginal deliveries) considering the low cost of oxytocin. Our results indicate that 51 women receiving 80 units of prophylactic oxytocin are needed to prevent 1 episode of use of additional oxytocin to hemorrhage after the first post-delivery hour; 21 are needed to prevent 1 episode of hematocrit decline greater than 6% units. Nevertheless, ongoing monitoring, evaluation and reporting of this use in larger populations will be necessary to further demonstrate the safety and the effectiveness (vis-à-vis outcomes such as our primary outcome and blood transfusion) of higher dose regimens for vaginal delivery.

An important consideration for the efficient use of 80-unit oxytocin dose for postpartum prophylaxis concerns its stability when concentrated in 500cc of crystalloid. While concentrations $\leq 80\text{U}/1000\text{cc}$ (i.e., ≤ 40 units/500cc) have been demonstrated to be stable for at least 7 days (and therefore a premixed bag can have a shelf-life of 7 days), no such data are available for the 80U / 500cc concentration.^{25–26} As a result, hospital pharmacies will typically accord no more than a 2-day shelf-life for premixed oxytocin concentration greater than 40 units in 500cc. Therefore, stability studies of high dose oxytocin regimens are needed to facilitate its efficient clinical use and evaluation. Since both the dose and duration of administration may play a role, future evaluation should also assess the effect of varying duration of administration particularly when given within 30 minutes.

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Figure 1.
Flow of patients through the oxytocin trial

Table 1

Baseline Characteristics of the Oxytocin Trial Population (n=1,798)

Characteristic	80 Units (n=658)	40 Units (n=481)	10 Units (n=659)
Race			
Black	379 (58)	278 (58)	404 (61)
White	156 (24)	97 (20)	143 (22)
Hispanic	120 (18)	101 (21)	106 (16)
Other	3 (<1)	5 (1)	6 (<1)
Prior cesarean delivery	30 (5)	27 (6)	29 (4)
Nulliparous	245 (37)	164 (34)	264 (40)
Body mass index			
Obese	360 (55)	285 (60)	391 (59)
Overweight	208 (32)	143 (30)	172 (26)
Normal and underweight	90 (14)	53 (11)	96 (15)
Age(mean $\pm$ SD)	24.4 ($\pm$ 5.5)	23.9 ($\pm$ 5.1)	23.9 ($\pm$ 5.4)
Hematocrit prior to delivery (mean $\pm$ SD)	33.5 ($\pm$ 3.6)	33.4 ($\pm$ 3.5)	33.6 ($\pm$ 3.4)
Preterm labor	83 (13)	47 (10)	58 (9)
Preeclampsia	75 (11)	50 (10)	93 (14)
Magnesium sulfate use	67 (10)	43 (9)	78 (12)
Oxytocin use in labor	561 (85)	406 (84)	560 (85)
▪ Induction	219 (33)	136 (28)	217 (33)
▪ Augmentation	342 (52)	270 (56)	343 (52)
Hydramnios	11 (2)	15 (3)	17 (3)
Chorioamnionitis	40 (6)	23 (5)	59 (9)
Amnioinfusion	106 (16)	74 (15)	119 (18)
Any Anesthesia	580 (88)	412 (86)	580 (88)
▪ Epidural	556 (85)	395 (82)	553 (84)
Prolonged second stage of labor	51 (8)	41 (9%)	30 (5)
Spontaneous membrane rupture	227 (35)	179 (37)	178 (27)
Singleton	653 (99)	477 (99)	655 (99)

SD, standard deviation.

Data are n (%) unless otherwise specified.

Table 2

Results for Primary Composite Outcome and its Components

Outcome	Outcome Frequency (%)			P-values Compared to 10U		
	80U (n=658)	40U (n=481)	10U (n=659)	80U	40U	Trend
Primary composite	42 (6)	31 (6)	45 (7)	0.745	0.798	0.744
Any uterotonic	40 (6)	30 (6)	45 (7)	0.580	0.691	0.578
Oxytocin	9 (1)	12 (2)	22 (3)	0.018	0.408	0.019
Other uterotonics	37 (6)	27 (6)	42 (6)	0.567	0.595	0.563
Methergine*	24 (4)	19 (4)	27 (4)	0.672	0.901	0.673
Hemabate*	19 (3)	13 (3)	23 (3)	0.533	0.453	0.525
Arterial ligation	1 (<1)	0 (0)	0 (0)	0.500*	n/a	0.366*
Hysterectomy	1 (<1)	0 (0)	0 (0)	0.500*	n/a	0.366*
Foley tamponade	0 (0)	1 (<1)	0 (0)	n/a	0.422*	1.000*
Arterial embolization	1 (<1)	0 (0)	1 (<1)	1.000*	1.000*	1.000*
Blood transfusion	5 (<1)	4 (<1)	7 (1)	0.564	0.768*	0.559

* Reflects exact test

Table 3

Results for Other Key Secondary Outcomes

Outcome	P-values for comparison to 10U					Trend
	80U (n=658)	40U (n=481)	10U (n=659)	80U	40U	
Hematocrit change *	4 (1-7)	4 (1-8)	4 (1-8)	0.074 [†]	0.249 [†]	0.080 [‡]
Hematocrit decline less than 6%	153 (23)	129 (27)	185 (28)	0.045	0.633	0.046
Hospitalization greater than 4 days	109 (17)	95 (20)	116 (18)	0.617	0.356	0.623
Fluid bolus	87 (13)	51 (11)	82 (12)	0.673	0.339	0.667
Diuretic treatment	1 (<1)	0 (0)	0 (0)	0.500 [§]	n/a	0.366 [§]
Pressor treatment	95 (14)	56 (12)	85 (13)	0.416	0.525	0.409
Pitocin discontinued	4 (<1)	6 (1)	3 (<1)	0.726 [§]	0.179 [§]	0.751 [§]
Estimated blood loss	401.3±190.5	405.0±137.8	413.1 ± 159.5	0.229	0.377	0.213
Blood loss greater than 500cc	24 (4)	24 (5)	38 (6)	0.070	0.568	0.072
Endometritis	8 (1)	1 (<1)	5 (<1)	0.402	0.410 [§]	0.346

Data are n (%) unless otherwise specified.

* Median (interdecile range)

[†] Wilcoxon rank-sum test

[‡] Jonckheere-Terpstra test

[§] Exact test

|| Mean ± standard deviation

Table 4

Estimates of the Primary Composite and Significant Secondary Outcomes

Outcome	80U Compared With 10U		40U Compared With 10U	
	RR	95% CI	RR	95% CI
Primary composite	0.93	0.62–1.40	0.94	0.61–1.47
Additional Oxytocin	0.41	0.19–0.88	0.75	0.37–1.50
6% or greater hematocrit drop	0.83	0.69–0.99	0.95	0.79–1.16

RR, relative risk; CI, confidence interval.