Open Access

Original Article

Comparison of Low and High Dosage Regime of Oxytocin for Uterine Contraction in Elective Caesarean Sections Performed Under Spinal Anaesthesia

Syed Ali Mazhar Rizvi, Azmat Riaz, Fatima Sharif Khan*, Tariq Mahmood Malik, Umairah Yaqub*, Muhammad Fawaz Amjad

Department of Anesthesia, Pak Emirates Military Hospital/National University of Medical Sciences (NUMS), Rawalpindi Pakistan, *Department of Gynecology/Obstetrics, Pak Emirates Military Hospital/National University of Medical Sciences (NUMS), Rawalpindi Pakistan

ABSTRACT

Objective: To compare low dose intravenous to high dose during elective Cesarean Sections.
Study Design: Quasi-experimental study.
Place and Duration of Study: Main Operation Theatre, Pak Emirates Military Hospital, Rawalpindi Pakistan, from Apr to May 2022.
Methodology: A total of two hundred term pregnant women were randomized to either 5 IU intravenous bolus group or 10 IU intravenous bolus group of Oxytocin. The difference in Hemoglobin levels (Pre-op minus post-op), tachycardia percentage, tone of uterus and need for additional "rescue" uterotonic doses/ agents, hypotension and post Oxytocin administration vomiting were assessed.
Results: The primary outcome was efficacy of both drugs in causing uterine contraction. There were 6(6.1%) patients in Low dose group who developed uterine atony while there were 5(5.3%) patients who developed uterine atony in group High dose. There were 18(18.4%) patients who developed partially inadequate uterine contraction in group LD versus 15(15.8%) patients in Group HD. There were 74(75.5%) patients who developed adequate contraction in group LD versus 75(78.9%) patients in group HD who developed adequate contraction with *p*-value of 0.850. The frequency of side effects was also comparable in both study groups. The estimated blood loss was as mean drop in hemoglobin was 1.77±.42 grams per deciliter in group LD versus 1.49±0.50 grams per deciliter in group HD with *p*-value of 0.469.
Conclusion: We concluded that use of low dose of oxytocin has similar efficacy in causing uterine contraction compared to high dose.

Keywords: Caesarean Section, Oxytocin and Uterine Contraction (MeSH Headings).

How to Cite This Article: *Rizvi SAM, Riaz A, Khan FS, Malik TM, Yaqub U, Amjad MF. Comparison of Low and High Dosage Regime of Oxytocin for Uterine Contraction in Elective Caesarean Sections Performed Under Spinal Anesthesia. Pak Armed Forces Med J 2025; 75(Suppl-2): S215-S220. DOI: https://doi.org/10.51253/pafmj.v75iSUPPL-2.11398*

INTRODUCTION:

Oxytocin belongs to a group of medicines called Oxytocics that act on the musculature of the uterus to make it contract.[1] It has numerous indications notable of which are to initiate and augment contractions during labor or childbirth, to help in the management of miscarriage, to prevent and control bleeding after delivery of the baby and during Caesarean sections.[2] As with all medications, oxytocin has numerous side-effects and incidence of these side effects is as high as 1-2%.[3] These include feeling of being sick, headache, tachycardia, bradycardia, irregular heartbeat, skin rashes, severe allergic reaction, difficulty in breathing, dizziness, cold & clammy skin and hypotension. In some patients Oxytocin also causes water intoxication the symptoms of which include headache, anorexia, nausea and vomiting, stomach pain, sluggishness, drowsiness, unconsciousness, hyponatremia, hypokalemia and fits.[4] Rare side-effects include chest pain, excessive or continuous uterine contractions, tearing of the womb, and sudden fluid overload of the lungs, sudden and brief sensation of heat all over the body, electrolyte imbalances, abnormal clotting, bleeding, disseminated intravascular coagulation and anemia.[5] The adverse effects on the baby due to excessive contractions include low blood salt levels, shortage of oxygen, suffocation & death.[6] Oxytocin has numerous drug interactions as well. It enhances the effects of Prostaglandins that may have been used to initiate labor. As per advisory, it should not be used for up to 6 hours after vaginal prostaglandin placement as the effect of both maybe enhanced.[7] Inhalational anesthetic agents like Halothane and Sevoflurane weaken Oxytocin induced uterine contractions and can potentially induce arrhythmias.[8] Oxytocin should also be used with caution in patients in whom the uterus is over-extended and more likely to tear, for example, in twin or triplet pregnancy and

Correspondence: Dr Syed Ali Mazhar Rizvi, Department of Anesthesia, Pak Emirates Military Hospital, Rawalpindi Pakistan
Received: 06 Jan 2024; revision received: 25 Mar 2024; accepted: 02 Apr 2024

in polyhydroamnios.[9] Oxytocin continues is an essential part of the armamentarium of the anesthetist and obstetrician to initiate and enhance uterine contractions after delivery of the baby and to prevent hemorrhage.[10] The complications of Oxytocin are dose related. Numerous protocols are followed world-wide regarding the dosage as well as method of administration for most efficacious results with minimum side effects. The current regimen being followed at Pak-Emirates Military Hospital (PEMH) is administering 10 IU Oxytocin intravenously as a bolus immediately after clamping of the placenta.[11] Unfortunately, a substantial number of patients develop tachycardia, hypotension, nausea, epigastric discomfort and vomiting within 5 minutes of Oxytocin administration.

The rationale of the study is to see whether reduction of Oxytocin to 5 IU bolus has any difference than using conventional 10 units by studying its effects and side effects.

METHODOLOGY

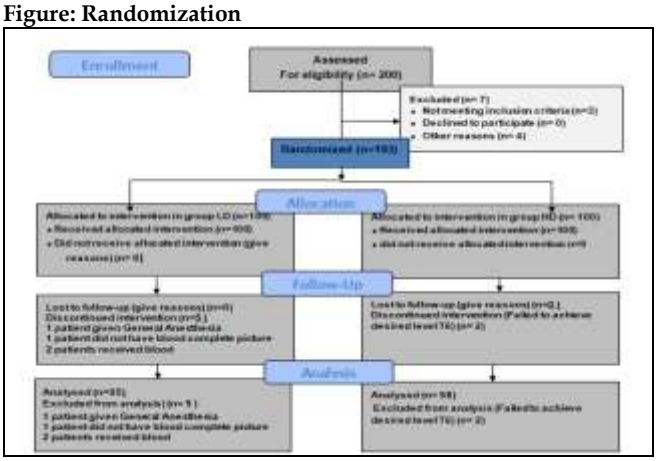
We initiated our Quasi-Experimental study after getting permission from hospitals ethical committee which acknowledged the authenticity of our research with IERB number A/28/EC/429/2022. The platform of our study was main operation theater of Pak Emirates Military Hospital, Rawalpindi Pakistan, which is a 1200 bedded hospital and the study duration was six months extending from Apr to Sep 2022. We calculated sample size with the help of WHO sample size calculator keeping level of significance 5%, power of test 80%, the anticipated efficacy of high dose oxytocin (10 units) to be 87%.[12] and anticipated efficacy of low dose oxytocin (5 units) to be 70%.[12] We collected a sample of 200 partiturens through non-probability consecutive sampling after taking consent of the patients and included 100 patients in each study group after randomizing the sample through sealed envelope technique.

Inclusion Criteria: We included Parturients who were 18 years to 40 years in age and were electively booked for Caesarean sections at term.

Exclusion Criteria: Patients with cardiac disease, renal disease, coagulopathies, severe pre-eclampsia, hepatic disease, gestation more than 5, pre-operative hemoglobin less than 9g/dl, emergency Caesarean sections, polyhydramnios, those operated under general anesthesia and patients who were in labor were also excluded.

All surgeries were performed under spinal anesthesia by consultant gynecologists and senior registrars (year 4 of FCPS training) only. Pre-op hemoglobin was measured with in 5 days prior to Caesarean section and post-op hemoglobin was sampled 48 hours after Cesarean section. All samples were sent after ensuring no intravenous fluids were administered within 6 hours of sampling. The patients were given 20ml/Kg of pre-load with help of a 16 gauge peripheral venous catheter and Spinal anesthesia was given by consultant anesthetist with help of 25 gauge spinal needle (Quincke,B.Braun, Pakistan). The dose of bupivacaine was same (15mg) and same intrathecal space (L3-4) was accessed in all patients. Adequate level (T6) was confirmed before incision and those patients who did not have adequate level of block were excluded from the study. Standard monitoring was attached to all patients including pulseoximeter, electrocardiogram, non-invasive blood pressure and surface temperature probe. The randomization of the sample was done in two groups marked as: Group HD and Group LD. The group HD was given 10 international units of oxytocin over a time interval of 60 seconds after clamping of cord and group LD was given 5 international units of oxytocin over 60 seconds after clamping of placental cord. For Uterine tone, gynecologist operating the patient was asked about degree of contraction on a scale of 1-10 after 5 minutes of the administration of oxytocin. An infusion of oxytocin containing 10 international units was given to all patients of both groups over three hours after bolus dose.

Figure: Randomization



The presence or absence of following side effects was recorded for all patients: Epigastric discomfort, tachycardia, hypotension, vomiting after adminis-

tration of respective Oxytocin doses. The dose of Oxytocin given to the patient was given by a different anesthetist. As estimation of blood loss in Caesarean section is difficult clinically, a difference in pre-operative and post-operative hemoglobin was calculated based on laboratory reports. Baseline mean Arterial Blood Pressure (MAP) and baseline heart rate was recorded just before administration of Oxytocin. This was recorded by the anesthetist in-charge of the case.

Hypotension was judged if there was greater than 20 percent reduction in mean arterial blood pressure.[13] Tone of the Uterus was measured at 5 minutes after the extraction of the baby. Assessment of uterine tone was done by the gynecologist of the case on a scale of 1-10 with 1-2 being Atony, 3-6 partially adequate contraction and 7-10 shows adequate contraction as displayed in Table-I. The need for additional doses of 2 international units of Oxytocin called as "Rescue doses" of Oxytocin were also documented for both groups and they were given on request of gynecologist.

Table-I: The Subjective Measurement of Uterine Contraction[14]

Uterine tone	Grades
Atony	1-2
Partially adequate contraction	3-6
Adequate contraction	7-10

Statistical Package for Social Sciences (SPSS) version 26.0 was used for the data analysis. Frequencies and percentages were calculated for qualitative variables. Mean and standard deviation were calculated for quantitative variable. Chi-square and t-test were used where appropriate. The *p*-value of ≤0.05 was considered statistically significant.

RESULTS

Total two hundred patients were included in the study and 98 patients completed the study protocol in high dose group and 95 patients completed the protocol in Low dose group. Two patients in high dose group did not have achieve T6 level and they were converted to general anesthesia while 1 patient in group Low dose was converted to general anesthesia due to inadequate level of spinal anesthesia and all of these patients were dropped from final results. Two patients in low dose group didn't have their blood complete picture done and therefore they were not included in final results. One patient in low dose had focal placenta accreta and one patient had dehiscence of scar, therefore they were excluded as B-lynch were applied in both patients along with blood transfusions. Rest of patients completed the study protocol and was included in final results. The demographic characteristics were similar in both study groups as we carefully designed the inclusion and exclusion criteria.

The primary outcome was efficacy of both drugs in causing uterine contraction. Six (6.1%) patients in Low dose group developed uterine atony while 5(5.3%) patients developed uterine atony in group High dose. Eighteen (18.4%) patients developed partially inadequate uterine contraction in group LD versus 15(15.8%) patients in Group HD, 74(75.5%) patients developed adequate contraction in group LD versus 75(78.9%) patients in group HD which was comparable with *p*-value of 0.850.

The frequency of side effects was also comparable in both study groups. Seventeen (17.9%) patients developed hypotension in group LD versus 14(14.3%) patients in HD with *p*-value 0.313. Frequency of tachycardia was 21(22.1%) in group LD versus 20(20.4%) in group HD with *p*-value 0.313. The frequency of nausea & vomiting was also analogous between both study groups. It was 18(18.9%) in group LD versus 15(15.3%) in group HD (*p*-value =0.315). 18(18.9%) patients developed epigastric pain in group LD versus 17(17.3%) patients in group HD. The rescue oxytotic was used in 12(12.6%) patients in group LD and 10(10.2%) patients in group HD with *p*-value of 0.381. The estimated blood loss was as mean drop in hemoglobin was 1.77±.42 grams per deciliter in group LD versus 1.49±0.50 grams per deciliter in group HD with *p*-value of 0.469. Blood transfusion was required in none of the patients. The primary outcome and side effects are presented in Table-II.

The demographics were comparable in both study groups. The mean age of patients was 28.88±4.07 years in group LD versus 29.30±3.80 years in group HD. The weight of patients was 67.89±2.6 kilograms in group LD versus 67.91±2.56 kilograms in group HD. The height of the patients was 152.76±3.37 centimeters in group LD versus 152.74±3.27 centimeters in group HD. The gestational age was 38.17±.89 weeks in group LD versus 38.23±0.90 weeks in group HD. The duration of surgery was 38.35±0.83 minutes in group LD versus 38.30±.74 minutes in group HD. The baseline mean blood pressure was 81.36±4.41 mm of Hg in group LD versus 81.16±4.70 mm of Hg in group HD. The baseline heart rate was 89.43±12.08 beats per minute in group LD versus 91.31±11.51 beats per

minute in group HD. The demographics are shown in Table-III.

Table-II: The Frequency of Different Grades of Uterine Contraction and Side Effects (n=193)

Parameter		LD group Frequency (%) n=95	HD group Frequency (%) n=98	*p*-value
Uterine tone	Atony	6(6.1)	5(5.3)	0.850
	Partially adequate contraction	18(18.4)	15(15.8)	
	Adequate contraction	74(75.5)	75(78.9)	
Hypotension	yes	17(17.9)	14(14.3)	0.313
	no	78(82.1)	84(85.7)	
Tachycardia	yes	21(22.1)	20(20.4)	0.313
	no	74(77.9)	78(79.6)	
Nausea & vomiting	yes	18(18.9)	15(15.3)	0.315
	no	77(81.1)	83(84.7)	
Epigastric pain	yes	18(18.9)	17(17.3)	0.459
	no	77(81.1)	81(82.7)	
Rescue oxytocin	yes	12(12.6)	10(10.2)	0.381
	no	83(87.4)	88(89.8)	
		Mean±SD	Mean±SD	
Decrease in hemoglobin concentration (g/dl)		1.77±0.42	1.49±0.50	0.469

LD=low dose &HD is high dose

Table-III: The Demographic Traits of Groups HD & LD (n=193)

Parameter		LD group Mean±SD n=95	HD group Mean±SD n=98	*p*-value
Age (years)		28.88±4.07	29.30±3.80	0.467
Weight (Kg)		67.89±2.6	67.91±2.56	0.971
Height (cm)		152.76±3.37	152.74±3.27	0.978
Gestational age (weeks)		38.17±0.89	38.23±0.90	0.609
Duration of surgery (minutes)		38.35±0.83	38.30±0.74	0.250
Baseline blood pressure (mm of Hg)		81.36±4.41	81.16±4.70	0.766
Baseline heart rate (beats per minute)		89.43±12.08	91.31±11.51	0.270
		Frequency (%)	Frequency (%)	
Parity	Primigravida	11(11.6)	16(16.3)	0.456
	Previous one scar	11(11.6)	5(5.1)	
	Previous two scars	37(38.9)	33(33.7)	
	Previous three scars	23(24.2)	33(33.7)	
	Previous four scars	13(13.7)	11(11.2)	

LD=low dose &HD is high dose

DISCUSSION

Oxytocin is by far the most common utero-tonic drug used for augmenting uterine contraction intra-operatively. It is used world-wide and has clear benefits for both maternal morbidity and mortality improvement. There is no conflict regarding use of oxytocin as utero-tonic drug of choice in cesarean delivery but the adequate dose of oxytocin is still subject of much debate. The dosing regimen of oxytocin is different for elective patients undergoing cesarean delivery as there is desensitization to oxytocin in non-laboring patients. In laboring patients uterus is sensitized to effect of oxytocin mediated by prostaglandin E and F.[15]

According to research of Balki *et al.,*[16] a continuous infusion of 3 international units per hour resulted in adequate uterine contraction in 30 women under study. They implied that minimum effective dose of oxytocin in 90% of individuals was 2.99 international units. How ever they used a smaller sample size and the patients were laboring who had cesarean delivery due to failed progress of labor. The presence of labor can be a confounding factor in their study as uterus is already sensitive to oxytocin[17] during labor and that is why minimum dose was adequate in most of the patients in their study.

Wei *et al.,*[18] compared 0.5 international unit of oxytocin to 0.25 international units in patients undergoing cesarean delivery under combined spinal-epidural anesthesia. They demonstrated that the minimum effective dose of oxytocin was 0.6 international units in young patients and 1.5 international units in older patients (age greater than 35). They used these trivial doses as initial dose and gave incremental doses to get desired level of uterine contractions. The doses they used are very small as compared to ours which we use in routine. They also demonstrated a strong associated between ages of partiturens with the frequency of side effects. They timed the bolus of oxytocin with the delivery of fetus and gave injection over five seconds. We gave injection upon cord clamping and gave it over one minute. The dose we used were quite higher in comparison. We chose to give 10 units of oxytocin as we are using this high dose as part of routine practice. The use of very small doses could have risen ethical concerns if patients would have gone into atony or post-partum hemorrhage. We were able to unveil that a dose as small as 5 international units can be useful and equitably effective to high dose. The next target could be a comparison of three units to 5 international unit so that standard dose can be premeditated and revised in our demographic population.

In operation theatre we usually avoid bolus doses of oxytocin during an episode of hypotension as

oxytocin as it potentiates hypotension.[19] We usually follow gynecologist led decision of oxytocin dose as they give more subjective assessment of uterine contraction and we rely on their judgment. How ever after literature surfing and conducting this study we have realized that we are using considerably high doses of oxytocin and there is irrefutable evidence in few studies that support low dose regime versus high dose regime. The uterine atony can have diverse causes but the first line treatment is usually same that is oxytocin bolus. According to a recent metanalysis performed to review doses of oxytocin for cesarean delivery comprising thirty-five studies it was revealed that bolus plus infusion regimes were better than bolus only regimes in causing adequate uterine contraction, the lower doses (<5 international units) reduced the adverse effects and higher doses (6-9 international units) did not offer much advantage over lower doses.[20]

The randomized controlled trial performed by Joseph *et al.*,[21] aimed at finding the dose of oxytocin which causes effective and optimal uterine contraction without adverse effects. They included ninety partiturients at term that underwent cesarean section under spinal anesthesia. They found that uterine contraction was adequate in sixty-six percent patients who received 1 international unit of oxytocin and was effective in eighty four percent patients who received 2 international units of oxytocin.

King *et al.*,[21] compared five units and 10 units of oxytocin followed by continuous infusion of 10 international units in five hundred milliliters of normal saline in next five hours. They did not find any significant difference of blood loss between both groups. However they were able to conclude that higher doses of oxytocin cause hemodynamic compromise. We compared 5 IU and 10 IU which is two times higher dose than 5 units and still we were unable to demonstrate a significant superiority of high dose regime than low dose regime. The use of very low doses that is from 1-3 units was not done to prevent the ethical concerns as the presence of post-partum hemorrhage could have been attributed to lose of oxytocin. It's the high time that we reconsider our practices of using high doses of oxytocin. The undesirable effects of this drug can lead to morbidity and mortality of the patients. The obstetricians need to be taken on board and need to be convinced with evidence for switching to low dose modules instead of high doses.

ACKNOWLEDGEMENT

I am thankful to my department for their assistance.

LIMITATIONS OF STUDY

We relied on subjective measurement of uterine contraction which could have been a source of bias.

CONCLUSION

We concluded that use of low dose of oxytocin has similar efficacy in causing uterine contraction compared to high dose.

Conflict of Interest: None.

Funding Source: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

SAMR & AR: Data acquisition, data analysis, critical review, approval of the final version to be published.

FSK & TMM: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

UY & MFA: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCE

1. Dujardin B, Boutsen M, De Schampheleire I, Kulker R, Manshande JP, Bailey J et al Oxytocics in developing countries Int J Gynaecol Obstet 1995; 50(3): 243-251.
2. Bhatu JJ, Chaudhari AB, Chauhan NR. Oxytocin versus Misoprostol used as an induction of labour in term in early rupture of Amniotic membranes. IJRCOG 2020; 9(3): 1023-1029.
3. Rogers C, Villar R, Pisal P, Yearley C. Effects of Syntocinon use in active management of third stage labour. Br. J. Midwifery 2011; 19(6): 371-378.
4. Wu Y, Wang H, Wu QY, Liang XL, Wang J. A meta-analysis of the effects of intramuscular and intravenous injection of oxytocin on the third stage of labor. Arch. Gynecol. Obste 2020; 301: 643-653.
5. Zeng Y, Zhang Y, Zhen M, Lao L, Ma Y, Liu L et al. Side-effects of oxytocin in postpartum hemorrhage: a systematic review and meta-analysis. Am. J. Transl. Res 2022; 14(3): 1934.
6. Eley VA, Culwick MD, Dennis AT. Analysis of anaesthesia incidents during caesarean section reported to webAIRS between 2009 and 2022. Anaesth Intensive Care 2023; 51(6): 391-399.
7. Arias F. Pharmacology of oxytocin and prostaglandins. Clin Obstet Gynecol 2000; 43(3): 455-468.
8. Dogru KU, Dalgic H, Yildiz KA, Sezer ZA, Madenoglu HA. The direct depressant effects of desflurane and sevoflurane on spontaneous contractions of isolated gravid rat myometrium. Int J Obstet Anesth 2003; 12(2): 74-78.
9. Aviram A, Salzer L, Hiersch L, Ashwal E, Golan G, Pardo J et al. Association of isolated polyhydramnios at or beyond 34 weeks of gestation and pregnancy outcome. OBGYN 2015; 125(4): 825-832.

10. Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, Cifkova R, Ferreira R, Foidart JM, et al. ESC Guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). Eur. Heart J 2011; 32(24): 3147-3197.
11. Somjit M, Surojananon J, Kongwattanakul K, Kasemsiri C, Sirisom M, Prawannoa K et al Comparison of low dose versus high dose of oxytocin for initiating uterine contraction during cesarean delivery: a randomized, controlled, non-inferiority trial. Int. J. Women's Health 2020: 667-673.
12. Cole NM, Abushoshah I, Fields KG, Carusi DA, Robinson JN, Bateman BT et al .The interrater reliability and agreement of a 0 to 10 uterine tone score in cesarean delivery. AJOG 2021; 3(3): 100342.
13. Mol A, Hoang PT, Sharmin S, Reijnierse EM, van Wezel RJ, Meskers et al Orthostatic hypotension and falls in older adults: a systematic review and meta-analysis. J Am Med Dir Assoc 2019; 20(5): 589-597.
14. Husslein P, Fuchs AR, Fuchs F. Oxytocin and the initiation of human parturition: I. Prostaglandin release during induction of labor by oxytocin. AJOG 1981; 141(5): 688-693.
15. Balki, Mrinalini, Ronayne, Michael D, Davies, Sharon M et alMinimum Oxytocin Dose Requirement After Cesarean Delivery for Labor Arrest. OB/GYN 2006; 107(1): 45-50.
16. Robinson C, Schumann R, Zhang P, Young RC. Oxytocin-induced desensitization of the oxytocin receptor. AJOG 2003; 188(2): 497-502.
17. Wei SQ, Luo ZC, Qi HP, Xu H, Fraser WD. High-dose vs low-dose oxytocin for labor augmentation: a systematic review. AJOG 2010; 203(4): 296-304.
18. Wang Y, Yuan J, Lin Y. Effect of phenylephrine on the prevention of oxytocin-induced hypotension. J. Anesth 2022: 5(8): 1-2.
19. Phung LC, Farrington EK, Connolly M, Wilson AN, Carvalho B, Homer CS et al. Intravenous oxytocin dosing regimens for postpartum hemorrhage prevention following cesarean delivery: a systematic review and meta-analysis. AJOG 2021; 225(3): 250-259.
20. Roopasree B, Joseph J, Mukkadan JK. Oxytocin-functions: An overview. MOJ Anat. Physiol 2019; 6(3): 128-133.
21. King KJ, Douglas MJ, Unger W, Wong A, King RA. Five unit bolus oxytocin at cesarean delivery in women at risk of atony: a randomized, double-blind, controlled trial. Anesth. Analg 2010; 111(6): 1460-1466.

.....