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ORIGINAL RESEARCH OBSTETRIC ANESTHESIA

Comparative hemodynamic effects of carbetocin vs oxytocin in mothers with stenotic valvular heart disease undergoing cesarean delivery: a randomized controlled trial

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ABSTRACT

Background & objective: Postpartum hemorrhage (PPH) is quite common an obstetric emergency, and is a nightmare for the anesthesiologist as well as the obstetrician. We compared the hemodynamic profiles of oxytocin and carbetocin for prevention of postpartum hemorrhage during elective cesarean delivery in patients with mild to moderate mitral or aortic stenosis.

Methodology: This randomized controlled trial included full term pregnant women with known mild to moderate mitral or aortic valve stenosis and undergoing elective cesarean delivery. After delivery of the shoulder of the baby, the participant received either oxytocin or carbetocin. Patients' hemodynamic parameters, including blood pressure, heart rate, cardiac output, and systemic vascular resistance, were recorded. The primary outcome was the 5-min average cardiac output after the drug administration. Secondary outcomes were cardiac output, systolic blood pressure, heart rate and systemic vascular resistance, blood loss, and the need for rescue uterotonics.

Results: Forty-five patients (23 patients in the carbetocin group and 22 in the oxytocin group) were analyzed. The 5-min average cardiac output after drug injection was comparable between the two groups. The number of participants needing rescue uterotonic boluses were significantly more in the oxytocin group than in the carbetocin group (P = 0.022).

Conclusion: In full-term pregnant women with stenotic valvular pathologies, carbetocin showed superior uterotonic effect compared to oxytocin; however, both drugs resulted in the equivalent hemodynamic effects.

Trial registration: Clinical trial registration with clinicaltrials.gov No. NCT05110482

Keywords: oxytocin; carbetocin; mitral stenosis; aortic stenosis; cesarean delivery; hemodynamics

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1. INTRODUCTION

Postpartum hemorrhage is the primary cause of nearly one quarter of all maternal deaths globally, and during cesarean delivery, uterotonic drugs are routinely recommended after the delivery of the baby to prevent postpartum hemorrhage.[1]

The first-line uterotonic drugs are oxytocin and its analogue, carbetocin.[1] Carbetocin has similar affinity for oxytocin receptors as the oxytocin but with a longer half-life.[2] Both drugs can cause peripheral vasodilatation and hypotension in addition to increased cardiac output mediated by an increase in heart rate and stroke volume.[3]

These hemodynamic derangements could be tolerated well by the non-cardiac patients but not the patients with cardiac diseases, for example stenotic valvular lesions. Patients with stenotic lesions have fixed cardiac output and would be less able to respond to the drop in the peripheral vascular resistance by increasing the cardiac output resulting in severe hypotension.[4]

Data from non-cardiac patients showed that both drugs had comparable hemodynamic effect.[3] However, there is lack of data regarding the hemodynamic effect of these drugs in patients with stenotic valvular lesions. We compared the hemodynamic profile of oxytocin and carbetocin used for prevention of postpartum hemorrhage during elective cesarean delivery in patients with mild to moderate mitral or aortic stenosis.

2. METHODOLOGY

Written informed consent was obtained from all participants. Institutional ethics committee approval No. MD-247-2020.

This randomized controlled trial included full term pregnant women aged 18-40 y with mild to moderate mitral or aortic valve stenosis and undergoing elective cesarean delivery. Exclusion criteria were severe mitral or aortic stenosis, concomitant regurgitant valve lesion, severe pulmonary hypertension, heart failure, hypertensive disorders of pregnancy, abnormal placentation, and bleeding disorder. Randomization was done using an online randomization tool. Group assignment according to randomization and drug preparation were placed inside sequentially numbered opaque envelops. An independent research assistant was responsible for opening the envelops and drug preparation.

Drug preparation was as follows: a 5-mL bolus syringe of either 1 IU of oxytocin or 100 µg of carbetocin. In the oxytocin group, a 50-mL syringe of 0.4 IU/mL of oxytocin was also prepared. In the carbetocin group, a 50 mL syringe of saline was prepared. Additional 5-mL syringes of 3 IU of oxytocin or 100 µg of carbetocin were prepared for use as rescue boluses if needed.

In the operating room, an 18-G intravenous canula was inserted and standard monitors were applied. Electrical cardiometry (ICON; Cardiotonic, Osypka; Berlin, Germany) was also attached.

Participants were pre-medicated with metoclopramide 10 mg IV. General anesthesia was induced via rapid sequence induction with ketamine 0.5 mg/kg, propofol 1 mg/kg, succinylcholine 1.5 mg/kg, lidocaine 2% 1.5 mg/kg IV. Cricoid pressure was applied until tracheal intubation and cuff inflation was performed. Maintenance of anesthesia was achieved by isoflurane 1.0-1.2% and atracurium 0.5 mg/kg then 0.1 mg/kg every 20 min.

After delivery of the shoulders of the baby the study drug was administered as follows; patients in the oxytocin group received oxytocin as a bolus of 1 IU followed by infusion with rate of 7.5 IU/h until the end of the procedure. While patients in the carbetocin group received a 100-µg carbetocin bolus followed by infusion of saline at the same rate as in the oxytocin group.

After drug administration, the obstetrician assessed the uterine contraction as either very good, good, sufficient, or atony. A rescue dose of the same drug as the group assignment (either 3 IU of oxytocin or 100 µg carbetocin) was given if the uterine tone was graded as

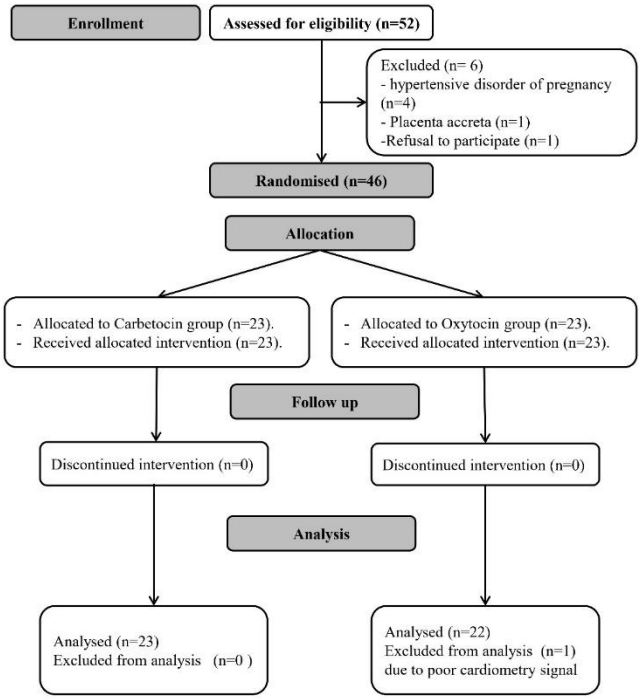


Figure 1: CONSORT flow chart

sufficient or atonic according to obstetrician assessment.

Patient's hemodynamic parameters, e.g., noninvasive blood pressure, heart rate, cardiac output, and systemic vascular resistance (SVR), were record at baseline before induction of anesthesia, and every 2-min after drug injection for 10 min, then every 5-min until the end of the procedure.

Intraoperative bradycardia (heart rate < 55 beat/min) was managed by 0.4 mg atropine IV. Hypertension was defined as systolic blood pressure >120% of baseline and was managed by administration of intravenous infusion of nitroglycerin 5 µg/min. Hypotension was defined as systolic blood pressure < 80% of baseline and was managed with intravenous bolus of 8 µg norepinephrine, repeated if hypotension persisted.

Further hemodynamic management was according to the discretion of the attending anesthetist.

The primary outcome was the 5 min average cardiac output after drug administration. Secondary outcomes were cardiac output, systolic blood pressure, heart rate and SVR, incidence of bradycardia, hypotension, hypertension, blood loss, and the need for rescue uterotonics. Patients' demographic data, type of lesion, and surgical data were recorded.

2.1. Sample size calculation

In a pilot study on 5 patients who received oxytocin, the 5-min average cardiac output after drug administration was 7.7 ± 0.8 L/min. We calculated a sample size which could detect at least 10% difference in the 5-min average cardiac output after the study drug administration between the two groups. The minimum number of mothers which was needed to have a study power of 80% and an alpha error of 0.05 was 34 patients (17 per group). The number was increased to 46 patients (23 per group) to compensate for dropouts.

2.2. Statistical analysis

Statistical Package for Social Science (SPSS) software, version 26 for Microsoft Windows (IBM Corp., NY, USA) was used for data analysis. Categorical data are presented as frequency (%) and were analyzed by the Chi square test. Continuous data were checked for normality using the Shapiro-Wilk test and are presented as mean ± standard deviation or median (quartiles) as appropriate. Continuous data were analyzed using the unpaired t-test or Mann-Whitney U test as appropriate. Repeated measures were analyzed using analysis of variance (ANOVA) for repeated measures. The Boneferroni test was used for adjustment for multiple comparisons. A P-value less than 0.05 was considered statistically significant.

Table 1: Demographic data and baseline hemodynamic characteristics

Variables	Carbetocin group (n = 23)	Oxytocin group (n = 22)	P-value
Age (y)	28 (23, 30)	28 (25, 31)	0.592
The primary Cardiac pathology			0.345
• Mild mitral stenosis	4 (17%)	9 (41%)	
• Moderate mitral stenosis	9 (39%)	6 (27%)	
• Mild aortic stenosis	7 (30%)	4 (18%)	
• Moderate aortic stenosis	3 (13%)	3 (14%)	
Previous cesarean delivery	6 (26%)	8 (36%)	0.457
Baseline heart rate (bpm)	98 ± 16	96 ± 10	0.574
Baseline systolic blood pressure (mmHg)	123 ± 17	122 ± 13	0.895
Baseline cardiac output (L/min)	7.6 ± 1.3	7.5 ± 1.2	0.687
Baseline SVR (dyn.sec.cm^{-}5)	931 ± 148	987 ± 196	0.292
Duration of procedure (min)	60 (45, 60)	50 (45, 60)	0.462

Data presented as median (quartiles), frequency (%), and mean ± standard deviation

Table 2: Intraoperative outcomes

Variables	Carbetocin group (n = 23)	Oxytocin group (n = 22)	P-value
5-min average cardiac output (L/min)	7.3 ±1.3	7.3 ± 1.0	0.910
Lowest cardiac output after drug administration (L/min)	7.2 (6.3, 7.9)	7.3 (6.6, 8.2)	0.040
Hypotension	8 (35%)	8 (36%)	0.809
Hypertension	2 (9%)	2 (9%)	1.000
Blood loss (mL)	700 (600,700)	650 (600, 700)	0.231
Rescue uterotonic	0 (0%)	5 (23%)	0.022

Data presented as median (quartiles), frequency (%), and mean ± standard deviation

3. RESULTS

Fifty-two mothers were screened for eligibility; six were excluded for not meeting the inclusion criteria. Forty-six mothers were included into this study and were randomized into the study's groups. One patient in the oxytocin group was not included in the analysis due to incomplete data, and 45 patients (23 patients in the carbetocin group and 22 in the oxytocin group) were available for the final analysis (Figure 1). Patients' demographic data and baseline hemodynamic characteristics were comparable between the two groups (Table 1).

The 5-min average cardiac output after drug injection was comparable between the two groups (Table 2). The cardiac output, systolic blood pressure and heart rate generally decreased after drug administration in both groups (Figures 2-4). On the other hand, the SVR generally increased in both groups after drug administration (supplementary file 1). The hemodynamic parameters, e.g., cardiac output, systolic blood pressure, heart rate and SVR, were comparablebetween the two groups up to 30 min after the drug administration (Figures 2-4) (supplementary file 1). The incidence of hypotension and hypertension was comparable between the two groups (Table 2). None of the patients developed bradycardia or tachycardia.

The number of participants needing rescue uterotonic bolus were more in the oxytocin group than in the carbetocin group (P = 0.022); however, the blood loss was comparable between the two groups, and none of the included mothers needed blood transfusion (Table 2).

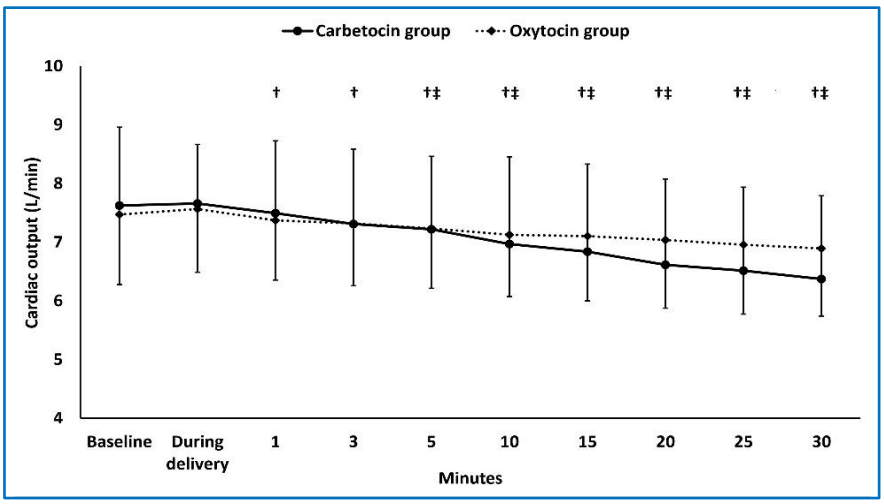


Figure 2: Cardiac output. † statistical significance compared to the baseline reading within the carbetocin group, ‡ statistical significance compared to the baseline reading within the oxytocin group

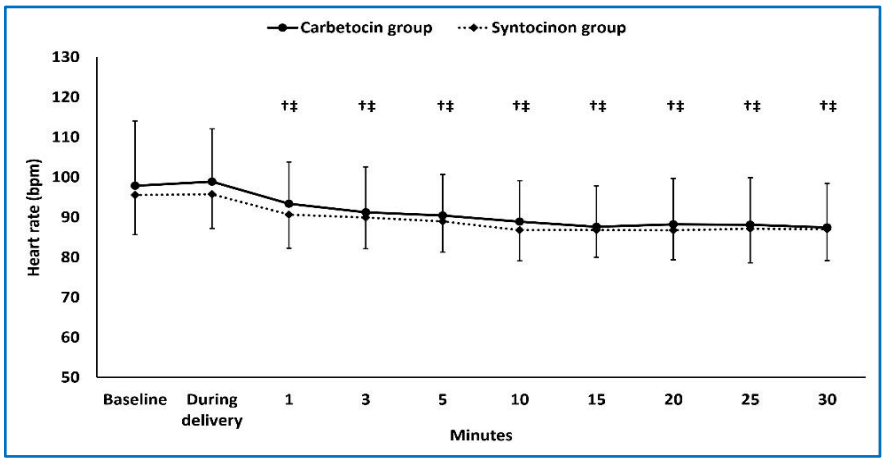


Figure 3: Comparative heart rates in the two groups

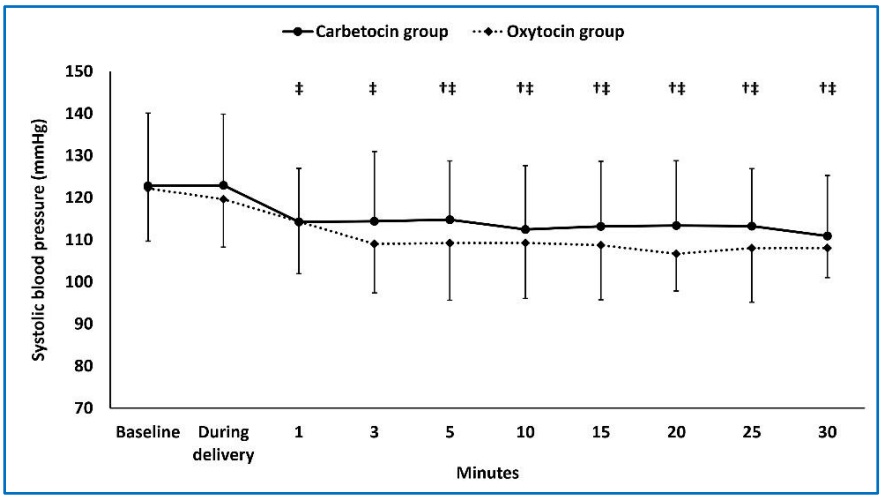
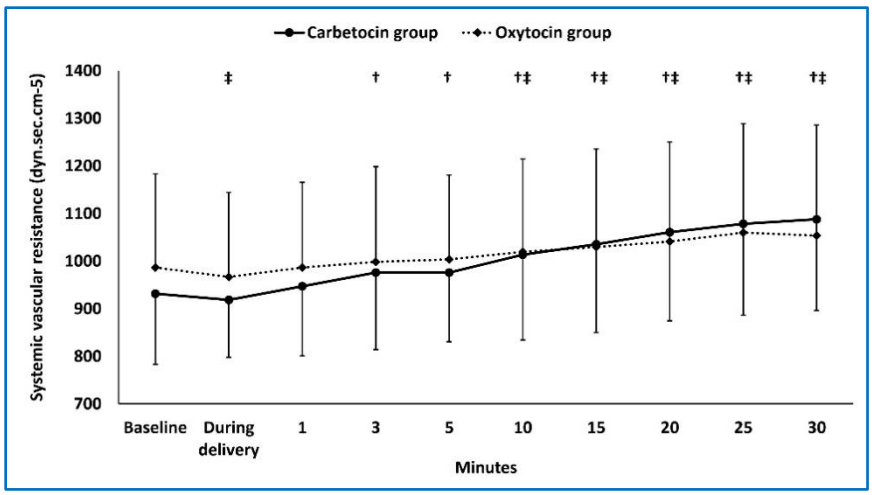


Figure 4: Comparative systolic blood pressures in the two groups



Supplementary file 1: Comparative SVR in two groups

4. DISCUSSION

The results of this study revealed that both study drugs, namely oxytocin and carbetocin, has comparable hemodynamic effects in. The two study groups had similar changes in blood pressure, stroke volume, cardiac output, and SVR. Furthermore, carbetocin showed superior results as a uterotonic compared to oxytocin. None of the patients who received carbetocin required additional rescue uterotonic drug while 22% of the patients who received oxytocin received an additional uterotonic bolus.

The two study drugs had been frequently compared in non-cardiac patients. Three recent meta-analyses showed that carbetocin is superior to oxytocin with regard to its uterotonic effect [5–7] In our patients, our results are in line with the current literature with regard to the uterotonic effect. Previous studies found similar hemodynamic effects for the two drugs [3, 8, 9]. However, all the available studies included mothers without cardiac pathologies. To the best of our knowledge, this is the first study which compared oxytocin and carbetocin in mothers with stenotic valvular lesions. Pisani et al compared the two drugs and found that oxytocin was associated with less hemodynamic stability compared to carbetocin [10]. Several other previous reports found that oxytocin decreases cardiac output and arterial blood pressure in healthy women [11, 12]. In our patients, oxytocin did not produce this effect, probably because we used a lower bolus dose than previous reports (1 U versus 5 U). Supporting this explanation, Sartain et al found that a 2 U bolus produces less hemodynamic effects compared to 5 U without the need to additional uterotonics [13]. Our oxytocin dose was close the that used by Sartain et al and this explains the stable hemodynamic profile in our patients after drug administration. The doses of the two drugs in our study were selected according to the international consensus for the use of uterotonic drugs.

Postpartum hemorrhage is the most common complication during childbirth and the leading cause of maternal mortality [14]. Prevention of postpartum hemorrhage primarily include managing uterine tone after delivery through controlled cord traction during placenta delivery in addition to routine administration of uterotonic drugs [1, 14]. Oxytocin and carbetocin are the first line drugs [1]; however, both drugs are associated with undesirable hemodynamic sequelae and their hemodynamic profile in patients with stenotic lesion is not well studied.

Our results support the current literature for the superiority of carbetocin over oxytocin considering the uterotonic effects. However, our findings did not favor the use of either of the two drugs in patients with stenotic cardiac lesions; thus, we suggest that the drug selection in these patients should be individualized according the desired uterotonic effect and the current surgical status and none of the two drugs provides additional advantage in the cardiovascular profile.

5. LIMITATIONS

The current study was a single-center study with limited number of participants. The study did not corelate the degree of valvular pathology with the parameters studied. We included patients with stenotic lesion without any other cardiac comorbidity; therefore, future studies are needed to assess the hemodynamic effect of these drugs in other cardiac lesions.

6. CONCLUSION

In conclusion, in full-term pregnant women with stenotic valvular pathologies, carbetocin showed superior uterotonic effect compared to oxytocin; however, both drugs produced equivalent hemodynamic effects.

7. Data availability

The numerical data generated during this research is available with the authors, and can be made available on a reasonable request.

8. Acknowledgement

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9. Conflict of interest

The authors declare no conflict of interests. The study utilized the hospital resources only, and no external or industry funding was involved.

10. Authors' contribution

All authors took part in the conduct of the study and preparation of this manuscript.

11. REFERENCES

1. Heesen M, Carvalho B, Carvalho JCA, Duvekot JJ, Dyer RA, Lucas DN, et al. International consensus statement on the use of uterotonic agents during caesarean section. Anaesthesia. 2019;74:1305–19. [PubMed] DOI: 10.1111/anae.14757
2. Hunter DJ, Schulz P, Wassenaar W. Effect of carbetocin, a long-acting oxytocin analog on the postpartum uterus. Clin Pharmacol Ther. 1992;52(1):60-7. [PubMed] DOI: 10.1038/clpt.1992.103
3. Rosseland LA, Hauge TH, Grindheim G, Stubhaug A, Langesæter E. Changes in blood pressure and cardiac output during cesarean delivery: the effects of oxytocin and carbetocin compared with placebo. Anesthesiology. 2013;119:541–51. [PubMed] DOI: 10.1097/ALN.0b013e31829416dd
4. Sliwa K, Johnson MR, Zilla P, Roos-Hesselink JW. Management of valvular disease in pregnancy: A global perspective. Eur Heart J. 2015;36:1078-89. [PubMed] DOI: 10.1093/eurheartj/ehv050
5. Onwochei DN, Owolabi A, Singh PM, Monks DT. Carbetocin compared with oxytocin in non-elective Cesarean delivery: a systematic review, meta-analysis, and trial sequential analysis of randomized-controlled trials. Can J Anaesth. 2020;67:1524–34. [PubMed] DOI: 10.1007/s12630-020-01779-1
6. Jaffer D, Singh PM, Aslam A, Cahill AG, Palanisamy A, Monks DT. Preventing postpartum hemorrhage after cesarean delivery: a network meta-analysis of available pharmacologic agents. Am J Obstet Gynecol. 2022;226:347–65. [PubMed] DOI: 10.1016/j.ajog.2021.08.060
7. Sun H, Xu L, Li Y, Zhao S. Effectiveness and safety of carboxytocin versus oxytocin in preventing postpartum hemorrhage: A systematic review and meta-analysis. J Obstet Gynaecol Res. 2022;48:889–901. [PubMed] DOI: 10.1111/jog.15174
8. Moertl MG, Friedrich S, Kraschl J, Wadsack C, Lang U, Schlembach D. Haemodynamic effects of carbetocin and oxytocin given as intravenous bolus on women undergoing caesarean delivery: a randomised trial. BJOG. 2011;118:1349–56. [PubMed] DOI: 10.1111/j.1471-0528.2011.03022.x
9. Mannaerts D, Van der Veeken L, Coppejans H, Jacquemyn Y. Adverse Effects of Carbetocin versus Oxytocin in the Prevention of Postpartum Haemorrhage after Caesarean Section: A Randomized Controlled Trial. J Pregnancy. 2018;2018:1374150. [PubMed] DOI: 10.1155/2018/1374150
10. Pisani I, Tiralongo GM, Gagliardi G, Scala RL, Todde C, Frigo MG, et al. The maternal cardiovascular effect of carbetocin compared to oxytocin in women undergoing caesarean section. Pregnancy Hypertens. 2012;2:139–42. [PubMed] DOI: 10.1016/j.preghy.2012.01.002
11. Langesaeter E, Rosseland LA, Stubhaug A. Haemodynamic effects of repeated doses of oxytocin during Caesarean delivery in healthy parturients. Br J Anaesth. 2009;103:260–2. [PubMed] DOI: 10.1093/bja/aep137
12. Secher NJ, Arnsbo P, Wallin L. Haemodynamic effects of oxytocin (syntocinon) and methyl ergometrine (methergin) on the systemic and pulmonary circulations of pregnant anaesthetized women. Acta Obstet Gynecol Scand. 1978;57:97–103. [PubMed] DOI: 10.3109/00016347809155884
13. Sartain JB, Barry JJ, Howat PW, McCormack DI, Bryant M. Intravenous oxytocin bolus of 2 units is superior to 5 units during elective Caesarean section. Br J Anaesth. 2008;101:822–6. [PubMed] DOI: 10.1093/bja/aen273
14. Shields Laurence, Goffman Dena, Caughey Aaron. Postpartum Hemorrhage ACOG practice bulletin: Clinical Management Guidelines for Obstetrician-Gynecologists. Obstet Gynecol. 2017;130:168–86. DOI: 10.1097/AOG.0000000000002351

