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The Hemodynamic Effects of Oxytocin and Carbetocin during Cesarean Delivery under Regional Anesthesia: A Double-Blinded, Randomized Study

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Abstract: ***Background: Oxytocin is a nine-amino-acid peptide generated in hypothalamic neurons and transferred down posterior pituitary axons before being secreted into the bloodstream. Oxytocin is also secreted from the brain and a few other tissues, including the testes and ovaries. Carbetocin is a long-acting synthetic analog of oxytocin that can be injected intravenously or intramuscularly as a single dose.Carbetocin has a half-life of about 40 minutes when administered intravenously, which is about 4–10 times longer than the half-life of oxytocin. Both drugs are used to prevent and manage post-partum hemorrhage (PPH); it has been recorded that both drugs had similar hemodynamic effects. This research aims to compare the hemodynamic effects of carbetocin and oxytocin throughout elective cesarean delivery under regional anesthesia in a double-blind, randomized controlled trial. Method: A total of 80 patients, ASA I underwent elective cesarean section under spinal anesthesia, were included in this research. The patients were randomly assigned to two evenly distributed groups. Group A received oxytocin (Syntocinon Novartis Pharmaceuticals Ltd.) (5 IU) as an IV bolus dose over 10 seconds in 10 ml 0.9% NaCl solution, and group B received carbetocin (PabalFerring pharmaceutical Ltd.) 100 µg as an IV bolus dose over 10 seconds in 10 ml 0.9% NaCl solution. Results: At the start of the study and the end of the operation, no statistically meaningful change in systolic, diastolic, mean of blood pleasure, or HR.As both drugs increased HR (p-value was 0.063) and decreased BP (P-value 0.109 in SBP, 0.326 in DPB, 0.343 in mean BP). Conclusion: This study concluded that iv administration of a bolus of both oxytocin (5 IU) or carbetocin (100 Mcg) over 10 seconds during the elective cesarean section for ASA I patients; have comparable hemodynamic effects (hypotension and tachycardia), and there was no statistically significant difference between the two drugs with the previous doses regarding MI symptoms, hypotensive effects, blood loss orHB difference levels pre and postoperative, and both drugs have the same good prophylactic effect from PPH.***

Keywords: Oxytocin, Carbetocin, Postpartum Hemorrhage

1. Introduction

Post-partum hemorrhage (PPH) is a potentially life-threatening complication in both cesarean and vaginal delivery. About 6% of all deliveries are affected by PPH ([1]). Since uterine atony is the most common cause of PPH, it is advised to control the third stage of labor actively [(2)]. Intravenous injection of 5 IU of oxytocin is prescribed as the drug of choice to minimize the frequency and seriousness of PPH ([3]). It does, though, have a relatively limited half-life.In contrast, carbetocin, an oxytocin analog that works through such molecular pathways like oxytocin, does indeed have a longer half-life that has been shown to reduce the need for extra oxytocin. To avoid PPH, 100 g of carbetocin is currently used daily (4).

Clinical studies comparing the contractile effects of carbetocin and oxytocin found that both medications caused similar harmful effects ([5]). However, to the extent of our knowledge, there is insufficient clinical data on carbetocin's hemodynamic side effects. Because of their usage as a prophylactic treatment and increasing amount of high-risk parturients, whether due to pre-existing cardiovascular disorder or pregnancy, it is critical to assess these medications' hemodynamic side effects ([6].

2. Method

This randomized controlled trial was carried out at Beni-Suef University Hospital with the approval of the anesthesia department and the local ethics and research committee. After obtaining informed written consent from the study's participants.This study was from 1/6/2016 to 31/1/2017.

All patients were prepared preoperatively by full history taking and examination. Routine investigations were revised (CBC, coagulation profile, liver and kidney functions test), and we gave (50 mg ranitidine IV, 10 mg metoclopramide IV for prophylaxis against aspiration.

Patients were given monitors as they arrived in the operation room, including a 5-lead ECG, non-invasive arterial blood pressure, and pulse oximetry. An 18-gauge intravenous cannula was implanted, and fluid preload (lactated ringer solution 10 ml/kg) was given. Under strict aseptic technique, spinal anesthesia was performed in the seated position, in the L3–L4 or L4–L5 space, with 3 ml heavy bupivacaine 0.5 percent (15 mg), and also patients were placed in supine position with left uterine displacement and supplemented with oxygen at 3 L/min.

The study included healthy pregnant women (ASA I) who underwent elective cesarean section at term under regional

anesthesia (spinal anesthesia). With exclusion criteria as follows.

1) Women refusing regional anesthesia
2) Contraindication of regional anesthesia (e.g., coagulopathy)
3) Women with conditions associated with an increased risk of PPH as placental abruption,placentapraevia, and multiple gestations.
4) Pregnancy-related complications like gestational diabetes, pre-eclampsia, and pre-existing problems such as cardiovascular, insulin-dependent diabetes, hypo-/hyperthyroidism, or kidney disease may interfere with hemodynamic parameters.

This study is a prospective, randomized, double-blind single-center study (ratio 1:1). The patients were divided into 2 groups at random using an invisible sealed envelope technique in a double-blind fashion, with 40 patients in each category receiving the study drugs as follows:

- Group (A): Patients were given oxytocin (Syntocinon Novartis Pharmaceuticals Ltd.) 5 IU as an IV bolus dose over10 seconds in 10 ml 0.9% NaCl solution.
- Group (B): patients were given carbetocin (PabalFerring pharmaceutical Ltd.) 100 µg as an IV bolus dose over 10 seconds in 10 ml 0.9% NaCl solution.

The study nurse's random list diluted either oxytocin or carbetocin into a 10 ml syringe with 10 ml 0.9 percent NaCl solution. Both drugs were completely ready five minutes before the cesarean delivery and gaveto the anesthesiologist. The researchmedication was given to patients after delivery of the baby and was double-blind to the clinical staff (anesthesiologists andobstetricians).

Primary outcome

1) Hemodynamic effect (blood pressure, heart rate) : After spinal anesthesia has been administered pre-operative, and in relation to relevant actions such as administering the study medication, delivering the child, and certainsurgery techniques such as exteriorization of the uterus (causing a raisedvenous return).
2) Symptoms of myocardial ischemia (as shortness of breath, chest pain, feeling of heaviness in chest pain)
3) Incidence of hypotension following drug administration.

Secondary outcomes

1) Demographic data (age, weight, BMI, gestational age, indication of cesarean section)
2) Intraoperative use of ephedrine (after the study drug administration)
3) The number of patients who require an additional dose of oxytocin or carbetocin.
4) Incidence of post-partum hemorrhage (PPH)
5) Measures to control post-partum hemorrhage (PPH) (if it happens).
6) Post-operative hemoglobin.
7) Intra-operative and post-operative evaluation of blood loss.
8) The need for blood transfusion will be recorded during 1st 24 hours after CS.

Statistical analysis

The statistical software package SPSS 13 was used for all analyses (SPSS Inc., Chicago, IL, USA). Means and standard divisions of the means were used to express the test findings. Independent samples Student's-test or chi-square test is used to compared demographic and clinical results.If the P-value was < 0.05, the differences were considered significant.

Report on Sample Size (power analysis)

Regarding hemodynamic changes, group sample sizes of 40 in group I and 40 in group II have an 80% potential to detect a 0.31 gap in group proportions (odds ratio of 4.4). In Group I, the null hypothesis predicts a value of 0.5, while the alternate hypothesis predicts a value of 0.81. Group II has a proportion of 0.5. The Fisher's exact test statistic is a two-sided test.

3. Results

This study included 80 patients with ASA I who underwent elective cesarean section under spinal anaesthesia.The patients were randomly allocated into two equally divided groups (40 patients each) using the closed envelope technique.Group A received oxytocin (Syntocinon Novartis Pharmaceuticals Ltd.) (5 iu) as an IV bolus doseover 10 seconds in 10 ml 0.9% NaCl solution, and group B received carbetocin (PabalFerring pharmaceutical Ltd.) 100 µg as an IV bolus dose over 10 seconds in 10 ml 0.9% NaCl solution.The statistical significance of the patients involved in this sample revealed no significant differences. The mean age was 25.70±3.39 & 25.88±3.49 years for group A and group B, respectively. The mean body weight was 81.75±8.05 & 82.13±8.54 kgs in group A and group B, respectively. The mean height was 162.50±5.88 & 164.50±6.08 cm in group A and B, respectively, and BMI means 30.73±1.74 in group A and 30.10±1.68 in group B respectively and gestational age range 37-40 weeks (Table 1).

Table 1: Comparison between group A and group B as regards demographic data

	Group A (No.=40)		Group B (No.=40)		Independent t-test	
	Mean	SD	Mean	SD	T	P-value
Age	25.70	3.39	25.88	3.49	-0.227	0.821
Weight	81.75	8.05	82.13	8.54	-0.202	0.840
Height	162.50	5.88	164.50	6.08	-1.496	0.139
BMI	30.73	1.74	30.10	1.68	1.636	0.106
Gestational age	38.28	1.01	38.15	1.08	0.535	0.594

Group A=oxytocine group, Group B=carbetocin group. The data are shown as mean±SD. There was no statistically significant demographic data between the studied groups at p-value >0.05.

In this study, no patients experienced myocardial ischemia symptoms (such as shortness of breath, chest pain, or a feeling of heaviness in the chest) or post-partum hemorrhage. Regarding the development of hypotension

following the administration of oxytocin or carbetocin, about 20 patients (50%) in group A and 17 patients (42%) in group B, respectively (Table 2)

Table 2: Comparison between group A and group B regarding symptoms of myocardial ischemia, the incidence of hypotension, additional drug use, and incidence of PPH

	Group A (No.=40)	Group B (No.=40)	Chi-square test				
	No.	%	No.	%	X^2	P-value	
Symptoms of MI	No	40	100.0%	40	100.0%	NA	NA
Incidence of hypotension after drug administration	No	20	50.0%	23	57.5%	0.453	0.50
	Yes	20	50.0%	17	42.5%		
Additional drug use	No	40	100.0%	40	100.0%	NA	NA
Incidence of PPH	No	40	100.0%	40	100.0%	NA	NA

Group A =Oxytocine group, Group B = Carbitocine group, The data are shownas number and percentage. No statistically significant difference in the incidence of hypotension after drug administration (P-value >0.05).

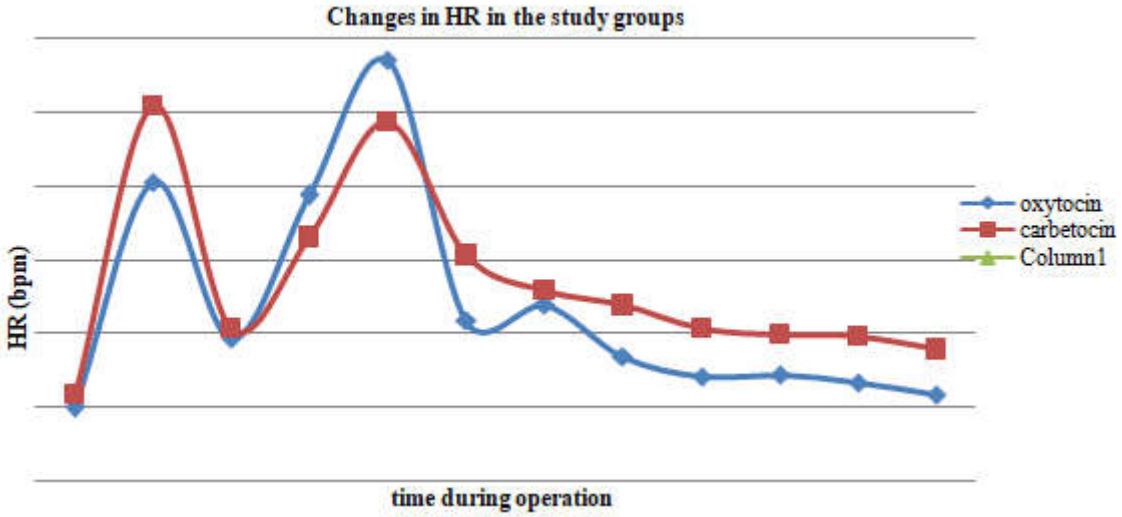
In this study, we used ephedrine in both groups as management of hypotension, in about 14 (35%) patient in group A and 15 (37.5%) patient in group B, respectively, with doses (10mg,15 mg, and 20 mg) as shown in table (3) .

Table 3: Comparison between group A and group B as regard use of ephedrine and dose of ephedrine

	Group A (No.=40)		Group B (No.=40)		Chi-square test	
	No.	%	No.	%	X^2	P-value
Use of ephedrine						
▪ No	26	65.0%	25	62.5%	0.054	0.816
▪ Yes	14	35.0%	15	37.5%		
➢ 10 mg	9	22.5%	5	12.5%		
➢ 15 mg	3	7.5%	4	10.0%	3.305	0.347
➢ 20 mg	2	5.0%	6	15.0%		

Group A= Oxytocine group, Group B=Carbitocine group. The data are shown as numbers and percentages. There was no statistically significant between the groups at P-value>0.05.

As regards the hemodynamic parameters, there was a rapid increase in HR immediately after drug administration and reach maximum at 1 minute after the administration of the study medication by 16.32 ± 2.51 bpm for the patients who received oxytocin and 14.51 ± 2.43 bpm for the patients who received carbetocin with apparent rebound bradycardia after 3 minutes (5.76 ± 1.87 bpm) for the patients who received oxytocin. In patients receiving carbetocin, the rebound bradycardia was less noticeable and late (2.04 ±1.75 bpm) at 5 min. No statistically significant difference in HR between groups studied (p-value was 0.063) (figure 1)



No statistically significant difference in systolic, diastolic, and mean of blood pleasure during the start of the research until the end of the operation P-value was (0.109 in SBP, 0.326 in DPB, and0.343 in mean BP).

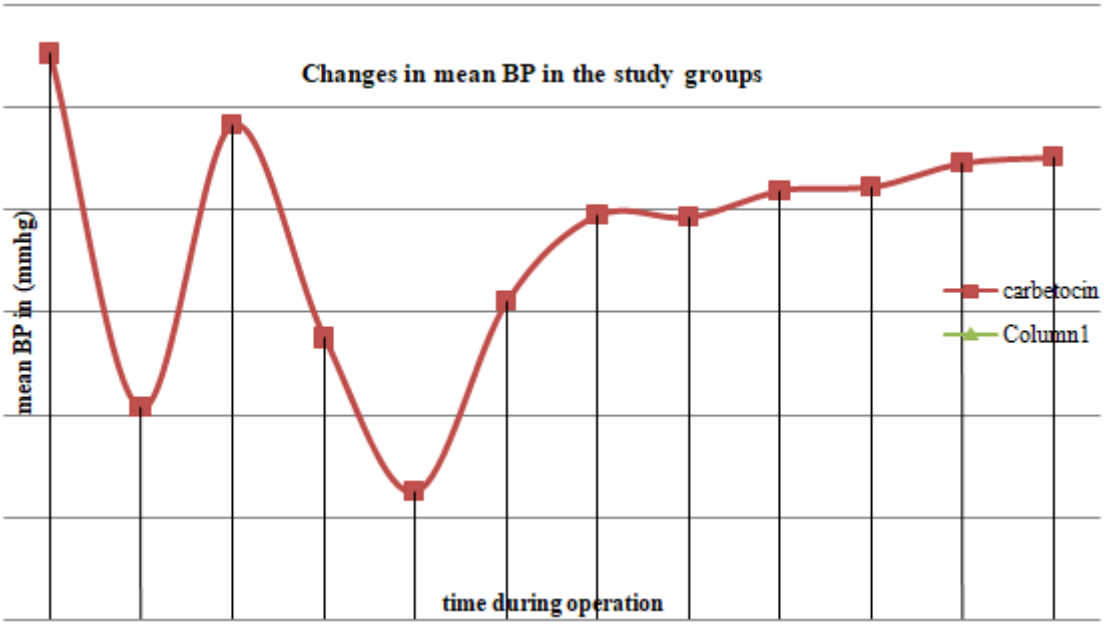


Figure 2: Change in mean blood pressure

The mean of blood loss intraoperatively was 675 ml for group A and 656ml for group B without significant difference between the two groups; the p-value was 0.444 (Table 4)

Table 4: Comparison between group A and group B as regard blood loss intraoperatively

	Group A (No.=40)		Group B (No.=40)		Independent t-test	
	Mean	SD	Mean	SD	T	P-value
Blood loss intra operative	675.00	109.19	656.25	108.71	0.770	0.444

Group A= Oxytocine group, Group B= Carbitocine group.The data are shown as mean±SD. No statistically significant difference in blood loss intraoperative between-group studied at P-value was >0.05.

In this study, both groups' patients did not suffer from blood loss postoperatively or need a blood transfusion during or after surgery.

No statistically significant difference between the studied groups regardingpre or post-operative hemoglobin; P-value >0.05. For group A the mean of pre-operative Hb was 11.14±0.55, and for group B, it was11.47 ±0.6.For group A the mean of post-operative Hb was10.19±0.55, and for group B, it was 10.37±0.55. Table (5) .

Table 5: Comparison between pre and post-operative HB for groups A and B.

	Pre-operative HB		Post-operative HB		Paired t-test	
	Mean	SD	Mean	SD	T	P-value
Group A	11.14	0.55	10.19	0.55	1.725	0.160
Group B	11.47	0.6	10.37	0.55	1.327	0.188

Group A= Oxitocine group, Group B=Carbitocine group, The data are shown as mean±SD. No statistically significant difference between the studied groups at P-value >0.05.

4. Discussion

This randomized, double-blind study aimed to compare the impact of clinically prescribed carbetocin (100 µg IV) versus oxytocin (5 IU IV) doses on maternal hemodynamic parameters throughoutelective cesarean delivery under spinal anesthesia.The findings revealed that no statistically significant variation in hemodynamic changes between thestudied groups.

There was nostatistically significant difference in blood loss between the two groupsstudied, with minimal HB deference in pre-operative and post-operative values in the two groups. We had no cases of PPH, and no blood transfusions were required intraoperative or post-operative.

The usage of uterotonic medications as a preventive measure has decreased maternal mortality and morbidity produced by PPH; nevertheless, oxytocin, the medication most commonly prescribed in the research (7), induces hemodynamic side effects of myocardial ischemia (8). Especially in large doses and in patients with hypovolemia or cardiac disorders, which are on the rise as the amount of deliveries with related risk factors rises. Previous research has shown that carbetocin, a synthetic oxytocin derivative with a longer half-life, better impacts uterine contraction than oxytocin [9].

In this study, both groups of patients had an increased HR while their BP values decreased by comparable levels immediately after drug administration; the rapid increase in HR by nearly one minute after applying the study medication, with apparent rebound bradycardia near the third minute for oxytocin. Recovering Patients who received carbetocin after 5 minutes had less pronounced and delayed bradycardia, but not statistically significant difference.

After one minute of receiving the study medication, the maximal hypotensive influence of the both drugs was achieved. The hemodynamic effects resolve to normal levels within a few minutes of drug administration, with slow

recovery in a patient treated with carbetocin in HR after the peak and more pronounced rebound bradycardia in a patient treated with oxytocin.By time acceptable clinical variation of HR and BP parameters observed, but these effects were no longer statistically significant. The incidence of hypotension due to drug administration was about 50% and 42.5% in groups A and B, respectively, but BP quickly returned to the normal values. Because the hypotensive effect of both drugs was concise; so we didn't use ephedrine for hypotension related to the effect of the drug, but we used ephedrine only for hypotension due to spinal anesthesia, which occurred in about 35% in the group (A) and 37.5% in the group (B) in doses ranges (10, 15 and 20 mg) iv bolus.

These results are consistent with the findings of a study conducted by Moert et al. ([10], which included 84 women and was conducted over 6 months. Hemodynamic parameters were measured noninvasively. To avoid PPH, measurements were done for 500 seconds after a slow intravenous bolus of clinically recommended doses of 100 ugcarbetocin or 5 IU oxytocin.They concluded that both drugs have comparable hemodynamic effects, with a peak effect at around 30–40 seconds.Both drugs improvedHR and reducedblood pressure (systolic, diastolic, and mean), with oxytocin causing more rebound bradycardia ([10].

Our findings are also consistent with the study which was done on high-risk patients for PPH. Multiple pregnancies, two or more previous cesarean sections, the presence of placenta previa, a previous myomectomy, uterine fibroids, fetal macrosomia, a history of PPH, and fetal malformations associated with polyhydramnios were all risk factors for primary PPH in 102 women undergoing elective cesarean section.Thecarbetocin group obtained a 100 µg IV bolus, while the control group received 20 IU oxytocin IV (150 mL/hour) in 1000 mL 0.9 percent NaCl solution. They came to the conclusion that a single injection of carbetocin with a similar hemodynamic profile is more effective than oxytocin in avoiding PPH than a continuous infusion (11).

Magedet al. [(12)] concluded that carbetocin is a safer alternative to oxytocin in the treatment of atonic PPH following vaginal delivery reduces post-partum blood loss and the need for additional oxytocics in a sample of 100 pregnant women who experienced vaginal delivery. There was no significant difference between the two sample groups in terms of side effects or hemodynamic changes.Systolic and diastolic blood pressures were measured immediately after the medication was administered and after 30 and 60 minutes [(12).]

Rosseland et al. (13) studied the hemodynamic effects of carbetocin and oxytocin on 76 patients after an elective cesarean delivery under spinal anesthesia. The primary outcome measure was the continuous measurement of invasive systolic arterial pressure. The mean of systolic arterial pressure dropped by 28 mmHg after oxytocin and by 26 mmHg after carbetocin. The drop was the most noticeable after 80 and 63 seconds. After 2.5 minutes, the differences were almost undetectable, though carbetocin had a significantly more substantial impact than placebo. The differences in systolic arterial pressure between groups reducedover 5 minutes and were disappeared after oneh. In all three groups, cardiac output and heart rate increased. They concluded that the hemodynamic influenceof oxytocin 5 U and carbetocin 100 µg were equal (13).

In their research, Attilakos et al. (9) randomized women to receive carbetocin 100 µg or oxytocin 5 IU intravenously after the baby was born.They discovered that the hemodynamic results were reassuring, with no clinically significant discrepancies between the two treatments. However, much of the hemodynamic changes caused by oxytocin arise during the first 5 minutes.Since it had previously been shown that the two medications had identical hemodynamic profiles, these study results did not provide constant hemodynamic monitoring throughout this period. However, sluggish intravenous application of oxytocics continues to limit their hemodynamic impact.

Rosales et al. (14) conducted a randomized clinical experimentalin a tertiary maternal hospital in Mexico, in which pregnant females with including at least 1 risk factor for PPH were randomly allocated to obtain carbetocin 100 µgas a single intravenous bolus of oxytocin 20 IU as a 6-h injection, all of which were administered shortly after delivery.PPH with blood loss greater than 500 mL was the main result.The amount of blood lost, extreme PPH (blood loss > 1000 mL), changes in hemodynamic and clinical variables within 24 hours of childbirth, and the need for additional uterotonictreatment.The hemodynamic results were considered to be reassuring, with no clinically relevant discrepancies between the two treatments.In addition, blood loss of more than 500mL was smaller in carbetocin-treated women than in oxytocin-treated women.The frequency of blood transfusions was comparable between groups (14).

Reyes et al. (15) studied 60 people with severe pre-eclampsia in a longitudinal, double-blind, randomized controlled trial.At the third period of labor, the women were randomly assigned to obtain either oxytocin or carbetocin.They concluded that carbetocin, rather than oxytocin, is a good substitute for preventing post-partum haemorrhage in women with severe pre-eclampsia.Given that it does not seem to have a major hemodynamic impact in women with severe pre-eclampsia and uses a lower amount per dose than oxytocin, it can be deemed a viable choice for managing the third stage of labor for women with hypertensive disorders of pregnancy (15).

Carbitocine and oxytocin were also tested for their efficacy in preventing PPH during emergency cesarean sections, and the results were similar to ours. El Beheryet al. (16) conducted a study on 180 pregnant women with a BMI of 30 who were randomly assigned to receive either oxytocin or carbetocin during C.S. within 24 h of delivery.The crucial performance metric was high primary PPH greater than 1000 m. They concluded that a single 100 µg IVcarbetocin infusion is more successful than an IV oxytocin infusion in obese nulliparous women experiencing emergency cesarean delivery to preserve sufficient uterine tone to avoidpost-partum bleeding.Both provide comparable protection and have minor hemodynamic effects (16).

Healthywomen undergoing Caesarean section (CS) under regional anesthesia can experience transient ECG

adjustments like ST-segment depression and T-wave abnormalities (17).

ECG variations are normal during and shortly after birth, and they're linked to tachycardia and systemic hypotension.Subjective symptoms such as chest pain or pressure, dyspnea, and headache have also been reported. Possible explanations include air emboli, cardiac sympathetic block, retroperitoneal traction pressure, and hyperventilation (18).It has been documented that intravenous oxytocin causes hypotension and tachycardia, and ECG modifications indicative of myocardial ischemia (18).

More research was needed to determine whether the cardiovascular impacts, ECG changes, and subjective symptoms experienced throughout CS were caused by oxytocin or by pregnancy, sympathetic block, surgery, or the profound physiological changes experienced during delivery. Svanstroet al. (8) observed 40 women who had elective CS under spinal anesthesia and were offered either 10 IU IV oxytocin or 0.2 mg methylergometrine.

As standard samples, ten fit, non-pregnant, non-anesthetized women (given 10 IU of oxytocin) were used.A 12-lead electrocardiogram (ECG), vectorcardiography (VCG), online computerized and intrusive arterial pressure were all registered.Based on significant ECG and STC-VM changes, they concluded that oxytocin administered as a 10 IU intravenous bolus causes hypotension, transient profound tachycardia, chest discomfort, and symptoms of myocardial ischemia (133).

They concluded that the effect is attributed to oxytocin administration instead of pregnancy, surgery, birth, or sympathetic block from spinal anesthesia. The cardiovascular effects of oxytocin seem to be temporary, and persistent myocardial damage appears to be unusual.They suggested starting with a low dose of oxytocin and gradually increasing it as a bolus or regulated infusion. If myocardial perfusion is impaired, hypovolaemia, coronary or major heart valve dysfunction, hypotension, or tachycardia is prevented, among other causes, rapid bolus injections can be avoided. (19).

There was no incidence of MI symptoms in our study. We excluded all patients with risk factors to MI symptoms like hypovolemic, hypotensive, anemic, and IHD patients. We used a small dose of oxytocin 5 IU, and the MI symptoms more likely in high oxytocin doses.

5. Conclusion

Our study concluded that iv administration of a bolus of both oxytocin (5 IU) or carbetocin (100 Mcg) over 10 seconds during the elective cesarean section for ASA I patients; have comparable hemodynamic effects (hypotension and tachycardia), and there was no statistically significant difference between the two drugs with the previous doses regarding MI symptoms, hypotensive effects, blood loss or HB differencelevels pre and post-operative. Both drugs have the same good prophylactic effect from PPH.

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