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Calcium Supplementation and Uterine Atony: Simple Solution to a Big Problem

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ABSTRACT

Objective: To compare the frequency of uterine atony in laboring women who are given prophylactic Calcium Chloride versus laboring women who did not receive it.

Study design: Quasi-experimental study

Place and duration of study: Pakistan Emirates Military Hospital Rawalpindi, Pakistan from Oct 2023 to Mar 2024.

Methodology: After getting approval of hospitals ethical committee, eighty-two gravid women at term, who were at the risk of development of uterine atony were recruited. The study participants were then divided into two groups. 41 patients were placed in Group-A, while 41 patients were placed in Group-C. The patients in Group-C were given one gram of Calcium Chloride (10ml of 10% Calcium Chloride solution) along with Oxytocin (10 international units) after cord clamping while Group-A patients were only given Oxytocin (10 international units) after cord clamping. The frequency of uterine atony was taken as the primary outcome.

Results: The uterine atony was present in 7(17.1%) Group-C patients in which supplemental calcium was administered, however 34(82.9%) patients did not develop uterine atony in contrast to Group-A where 15(38.5%) patients developed uterine atony, and twenty-four (61.5%) patients did not develop atony with *p- value* of less than 0.05.

Conclusion: The Intravenous administration of Calcium Chloride can prevent uterine atony during delivery in patients at risk of developing post-partum hemorrhage.

Keywords: Calcium chloride, cesarean section, spontaneous vaginal delivery, post-partum hemorrhage and uterine atony

How to Cite This Article: *Yaqub U, Saleem U, Parveen S, Khan S, Khalil AA, Rizvi SAM. Calcium Supplementation and Uterine Atony: Simple Solution to a Big Problem. Pak Armed Forces Med J 2024; 74(6): 147-151. DOI: https://doi.org/10.51253/pafmj.v74i6.11986*

INTRODUCTION

Uterine atony is failure of uterus to contract adequately after placental delivery. It is life threatening obstetrical emergency which is leading cause of post-partum hemorrhage, and it is accountable for thirty percent maternal deaths during immediate post-partum period[1] .The association of post-partum hemorrhage to uterine tone is due to incomplete mechanical compression of spiral arteries. The spiral arteries are deficient in muscle mass, and they depend solely on uterine contraction for closure. During contraction these are mechanically squeezed between crisscross organizations of uterine muscle fibers. If the uterine tone is not adequate, they are not squeezed and continue to bleed resulting in post-partum hemorrhage[2].The uterine atony is heralded by flaccid, large, and toneless uterus with increased blood loss. Uterine atony can be diffuse or focal. In diffuse atony whole uterus is flaccid and in focal atony lower segment is atonic and becomes dilated[3].

There are various risk assessment tools devised to identify the patients who are predisposed to uterine atony. The predisposing factors of uterine atony are identified as high body mass index, chorioamnionitis, hypertensive disorders, multiple gestations, diabetes mellitus, placenta accreta spectrum disorders, prolonged labor, and general anesthesia[4].There are several prophylactic strategies which have been used with variable success rate to prevent uterine atony and post-partum hemorrhage which can complicate both vaginal deliveries and cesarean sections alike. The pharmacological uterotonics are oxytocin, misoprostol and ergometrine[5].The interventional strategies include uterine message, uterine artery ligation, B-lynch sutures, balloon tamponade, internal iliac artery ligation and cesarean hysterectomy. Most of mild to moderate cases respond to uterotonic drugs and uterine message but some cases require escalation in form of surgical interventions[6].Despite all these management techniques, the incidence of uterine atony is still very high.

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Received: 31 Mar 2024; revision received: 30 Jul 2024; accepted: 29 Aug 2024

Serum calcium levels have been investigated recently to be linked to uterine atony as calcium is principal electrolyte responsible for maintenance of tone of muscles and blood vessels and has role in muscle contraction[7] .According to Hart BF intravenous calcium gluconate reduced post-partum hemorrhage in patients who did not respond to routine uterotonic drugs. They demonstrated that combination of calcium and quinine was more effective[8].The role of calcium in prevention of uterine atony was reinforced by findings of Muhammad Abdelgayed et al., [9], who established that low serum calcium levels have a strong association with uterine atony and calcium should be considered a risk factor of uterine atony[9].However there is a conflicting evidence to disprove the role of calcium in uterine atony as M K Farber el al demonstrated that co-administration of calcium and oxytocin did not affect uterine tone and blood loss[10].Therefore is study aimed to explore the effect of calcium on uterine tone for prevention of post-partum hemorrhage in vulnerable laboring women of our population.

METHODOLOGY

After grant of approval of ethical committee of hospital with IERB number ERC/554/23, a Quasi-experimental study was conducted at Pakistan Emirates Military Hospital (PEMH), Rawalpindi from October 2023 to March 2024. The sample size was calculated with the help of WHO sample size calculator keeping anticipated population proportion to develop uterine atony with calcium supplementation at 20%11 and anticipated population proportion to develop uterine atony without calcium supplementation to be 50%11. The sample came out to be 39. To address the potential dropouts the sample size was increased to 82 patients. The patients were recruited by non-probability consecutive sampling. The sample was divided into two equal groups (Figure).

Inclusion Criteria: Full term pregnant patients (38 plus weeks) of age 18 to 45 years who were at risk of uterine atony and post-partum hemorrhage on basis of risk factors derived from AWHONN (Association of Women's Health, Obstetric and Neonatal Nurses) tool 12 and were subjected to elective or emergency cesarean delivery were included.

Exclusion Criteria: The patients given general anesthesia, patients with blood dyscrasias, patients who were on anti-platelet therapy and patients with co-morbidities were excluded from the study.

All the patients for elective cesarean were booked from Gynecology and Obstetrics out-patient department and were evaluated thoroughly. The patients fulfilling the inclusion criteria who came to operation theatre for emergency cesarean section were also included. In operation theatre both patients (elective and emergency surgery) were randomized through a sealed envelope. Randomization plan is shown in Figure-1. Two groups were formulated named as: Group-C and Group A. All patients were given standard Spinal anesthesia. All Group-C patients were given one gram of Calcium Chloride (10ml of 10% Calcium Chloride solution) along with Oxytocin (10 international units) after cord clamping. The Group-A patients only received Oxytocin (10 international units) after cord clamping as practiced in routine. Following details were recorded: Age, Weight, Height, Body Mass Index and Type of Surgery. The primary outcome was frequency of uterine atony. The uterine atony was defined as: Presence of flaccid uterus along with post-partum hemorrhage (blood loss of greater than 1000 ml)[13].

The data was analyzed with help of statistical package of social sciences (SPSS) version 26.0. For quantitative variables means and standard deviation was calculated and for qualitative variables frequency and percentages were calculated. T-Test and Chi-square were applied where required. *p value* less than 0.05 was considered significant.

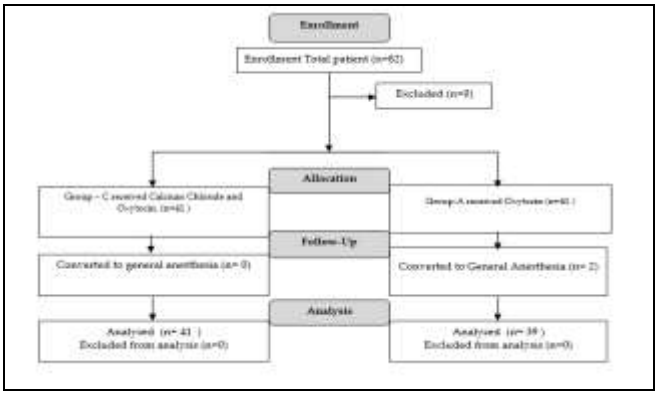

Figure: Consort Flow Diagram of Study Protocol

RESULTS

There was total eighty-two patients in the study groups, but eighty patients were included in final statistics to prevent bias as two patients in Group-A were converted to general anesthesia. The primary outcome was frequency of uterine atony in both study groups. The demographic characteristics and

secondary outcomes were similar in both study groups as presented in Table-II.

Table-I: Comparison of Demo Graphics And Key Parameters Among Study Groups (n=80)

		Group C (Calcium Chloride & Oxytocin) n=41 Frequency (%)	Group A (0xytocin alone) n=39 Frequency (%)	*p* value
Age (years)		29.04±3.44	28.0±3.70	0.721
Weight (Kg)		68.82±4.89	69.89±5.33	0.611
Height (cm)		159.97±17.55	158.89±17.4	0.858
BMI (Kg/m2)		26.04±2.42	26.51±2.41	0.143
		Frequency (%)	Frequency (%)	
Parity	1	8(19.5)	4(10.3)	0.350
	2	16(39.0)	20(51.3%)	
	3	7(17.1)	8(20.5%)	
	4	2(4.9)	1(2.6%)	
	5	4(9.8)	3(7.7%)	
	6	2(4.9)	2(5.1%)	
	7	2(4.9)	1(2.6%)	
Previous vaginal delivery	>4	6(14.6)	3(7.7%)	0.235
	>5	0(0)	2(5.1%)	
	>6	2(4.9)	1(2.6)	
	None	33(84.6)	33(84.6)	
Previous cesarean delivery	1	10(24.4)	5(12.8)	0.541
	2	14(34.1)	19(48.7)	
	3	7(17.1)	8(20.5)	
	4	2(4.9)	1(2.6)	
	None	8(19.5)	6(15.4)	
Frequency of risk factors in a patient	1	10(24.4)	11(28.2)	0.502
	2	22(53.7)	16(41.0)	
	2	9(22.0)	12(30.8)	
Other Risk factors	Labor induction	7(17.1)	5(12.8)	0.414
	Previous PPH	16(39.0)	14(35.9)	0.477
	Polyhyramnios	11(26.6)	10(25.6)	0.553
	chorioamnionitis	4(9.8)	8(20.5)	0.151
	Uterine fibroid	7(17.1)	6(15.4)	0.553
Type of surgery	Emergency	14(34.1)	14(35.9)	0.525
	Elective	27(65.9)	25(64.1)	

Table-II: Comparison Analysis of Uterine Atony between Study Groups (n=80)

outcome		Group C n=41 Frequency (%)	Group A n=39 Frequency (%)	*p*-value
Uterine atony	Yes	7(17.1)	15(38.5)	0.009
	No	34(82.9)	24(61.5)	

The mean age in patients of Group-C and Group-A were 29.04±3.44 years and 28.0±3.70 years respectively. The mean weight of patients in Group-C was 68.82±4.89 kg, mean height was 159.97±17.55 cm and mean body mass index (BMI) was 26.04±2.42 (Kg/m2). The mean weight of Group-A patients was 69.89±5.33 kg and mean height was 158.89±17.4 cm both of which corresponded to a BMI of 26.51±2.41 Kg/m2. The demographic parameters were similar with *p* value of less than 0.05. Most of the patients in Group-C and Group-A had parity of 2. Six (14.6%) patients in Group-C had greater than four normal deliveries and 2(4.9%) patients had greater than five normal vaginal deliveries. Three (7.7%) patients in Group-A had greater than 4 normal deliveries, 2(5.1%) had greater than 5 normal deliveries and one (2.6%) patient had greater than six deliveries. 33(84.6%) patients in Group-C never had vaginal delivery and 33(84.6) in Group-A never had any vaginal delivery with *p value* of 0.235. Ten (24.4%) patients in Group-C had previous one cesarean section, 14(34.1%) patients had previous two cesarean sections, 7(17.1%) had previous three sections and 2(4.9%) patients had previous four cesarean sections. Five (12.8%) patients in Group-A had previous one scar, 19(48.7%) had previous two scars, 1(2.6%) patient had previous three scars and 1(2.6%) had previous four scars. In Group-C, labor induction was done in 7(17.1%) patients, history of post-partum hemorrhage was found in 16(39.0%) patients, polyhydramnios was present in 11(26.6%) patients, chorioamnionitis was present in 4(9.8%) patients and uterine fibroid was a risk factor in 7(17.1%) patients. In Group-A, labor induction was done in 5(12.8%) patients, history of post-partum hemorrhage was found in 14(35.9%) patients, polyhydramnios was present in 10(25.6%) patients, chorioamnionitis was present in 8(20.5%) patients and uterine fibroid was a risk factor in 6(15.4%) patients.

The uterine atony was present in 7(17.1%) Group-C patients in which supplemental calcium was administered and 34(82.9%) patients did not develop uterine atony in contrast to Group-A where 15(38.5%) patients developed uterine atony and twenty-four (61.5%) patients did not develop atony with p value of less than 0.05 as shown in Table-III.

DISCUSSION

In this study Calcium Chloride administration prevented uterine atony in 82.9 percent of patients who had risk of developing post-partum hemorrhage. The patients who did not receive Calcium Chloride

had considerably high (38.5%) frequency of uterine atony. Though its sounds like a simple solution to a big problem, but role of calcium in prevention of uterine atony speaks volume. The association of serum calcium levels and uterine atony was highlighted by Premalahta et al., in a prospective cohort study in 2016. They performed serum calcium levels during post-partum period in two hundred patients who were admitted in their first and second stage of labor. Premalahta et al., followed the patients till delivery which was either vaginal or cesarean and they observed them for development of uterine atony in prospective fashion. They found that patients with adequate serum calcium levels had lower relative risk of development of uterine atony[14].

Uterine contractility is a complex phenomenon, and it exhibits dynamicity. Uterine myometrium undergoes peristalsis throughout the menstrual cycle which is wave like contraction, and it also undergoes sustained contractions which are focal in nature and are responsible for sloughing off endometrium. Regardless of the presence or absence of pregnancy, uterine myometrium has ability to contract, and this contraction is synchronized by intracellular calcium. The elevation in calcium levels of uterine myocytes modulates contraction and there are two sources of calcium influx. Therefore, it does not seem surprising to relate serum calcium levels to uterine tone and contractility[15]. The association of calcium and uterine tone is reinforced by the fact that calcium antagonists are employed for tocolysis[16]. Magnesium is anticonvulsant of choice in pre-eclampsia and association of high magnesium levels is established with risk of uterine atony. The mechanism suggested for this action of magnesium is due to antagonization of calcium at cellular level resulting in interference with actin-myosin interactions and myometrial relaxation.[17] Thus calcium is linked to uterine tone and its reduction can affect uterine tone.

According to another observational study by Oguaka VN it was found that hypocalcemia was associated with primary post-partum hemorrhage. Sixteen (11.4) patients who underwent spontaneous vaginal delivery developed PPH who had low serum ionized calcium levels[18]. However they performed observational study, and we performed quasi-experimental study. We performed our study with laboring women who were at moderate risk of development of post-partum hemorrhage. We did not include the patients at high risk of development of post-partum hemorrhage to avoid ethical concerns.

In another case-control study by Khan et al. sixty-eight percent patients who developed uterine atony had vitamin D deficiency. The mean age of patients in their study was relatable to our study sample. This association seems to have significant correlation as vitamin D is crucial in calcium homeostasis of the body and it can also be an important link in the chain[19]. According to a randomized controlled trial by Abd El-Samie et al., calcium was found to be equivalent to Methergine and better than Misoprostol in treatment of post-partum hemorrhage. Calcium also had added advantage of lower side effects and easily availability according to them calcium was used prophylactically and found to be a reliable uretrotonic[20].

ACKNOWLEDGEMENT

Obstetrics and gynecology department PEMH.

LIMITATION OF STUDY

The use of calcium as ureteronic is newer in practice of gynecology and obstetrics. We performed quasi-experimental study but there is need of randomized controlled trial on this subject. We did not include high risk patients to prevent ethical issues.

CONCLUSION

The intravenous Calcium Chloride administration can prevent uterine atony during cesarean delivery in patients at risk of developing post-partum hemorrhage.

Conflict of Interest: None.

Funding Source: None.

Authors Contribution

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

UY & US: Data acquisition, data analysis, drafting the manuscript, critical review, approval of the final version to be published.

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

AAK & SAMR: 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.

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