Correlation of Calcium Ion Levels and Postpartum Blood Volume

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***Abstract*—**
Background: Post partum hemorrhage is blood loss during vaginal delivery which around 500 mL or more than 1000 mL in cesarean section.
Objective: The purpose is to assess the correlation of calcium ion levels with post partum blood volume at RSUP H Adam Malik and networking hospital in Medan.
Methods: This study is an analytical study with case series, begin May - June 2022 in pregnant women in RSUP Haji Adam Malik and networking hospital with inclusion criteria. Postpartum blood volume using a pictogram and ion calcium levels were measured. Results is significant if p<0.05 with a 95% CI.
Results: There were 22 patients around 21-35 years old (88%), 12 patients (48%) were primiparous.Mean of gestational age was 38-40 weeks. The majority (44%) had 4 antenatal care visits. All patients (100%) didn't take calcium supplementation. There were 20 patients (80%) had > 23.5 cm upper arm circumference. There were 13 patients (52%) had 250-500 cc blood loss. There were 23 patients (92%) in hypocalcemic condition. Spearman correlation test showed a weak negative correlation between postpartum bleeding and ion calcium level.
Conclusion: There is no correlation between ion calcium level with postpartum blood volume.

***Keywords*: Calcium Ion levels, postpartum blood volume, pregnant women, age, parity, antenatal visits**

I. INTRODUCTION

Bleeding is something that always occurs in every delivery either spontaneous vaginal birth (SVB) or sectio caesarean (SC). Blood loss is estimated to be around 300-500 mL in SVB and 600-1000 mL in CS.[1] Total 27.1% of maternal deaths were caused by bleeding.[2] In Indonesia on 2020, as many as 1330 cases maternal death due to bleeding.[3] As many as 80% cases of postpartum bleeding occur in mothers who have risk factors.[4] Identification of postpartum bleeding risk factors as early as possible will help health workers in preventing or preparing themselves if there is a possibility of postpartum bleeding in patients who are ready to give birth.[5]

Hypocalcemia is one of postpartum bleeding risk factors. In Epstein et al (2020) study found that mothers with hypocalcemic conditions were significantly 8.9 times higher risk of experiencing severe postpartum bleeding. In this study it was also found that parameters of calcium ions or combined with fibrinogen levels can identify pregnant women with postpartum bleeding risk.[6] In another study, postpartum hemorrhage conditions caused by uterine atony had significantly lower calcium ion levels (1.0±0.35 mmol/L) than postpartum hemorrhage caused by other causes (1.12±0.28 mmol/L). and also in cases of labor without postpartum hemorrhage (1.11 ± 0.25 mmol/L). Calcium is needed for uterine contraction, therefore if blood calcium levels decrease, this can certainly interfere uterine contraction which will increase uterine atony risk.[7] In addition, adequate blood calcium levels can help increase oxytocin efficacy in increasing uterine contractions.[8]

Hypocalcemia conditions reported in different countries have different prevalences. The condition of hypocalcemia in India reached 66.4%,[9] Malaysia reached 26.0%[10] and Nigeria reached 29.20%.[11] In Indonesia, especially in the city of Jakarta, 25.2% of pregnant women in first trimester experience hypocalcemia.[12] The high prevalence of hypocalcemia increase incidence of PPH which also increase the risk of maternal death during childbirth. The World Health Organization (WHO) recommends that populations with low calcium intake take 1.5-2.0 g of calcium supplementation orally to reduce the risk of pre-eclampsia.[13]

The purpose of this research is to overview hypocalcemia prevalence in pregnant women at Medan and also correlation of hypocalcemia as a predictor of blood loss volume during delivery , so that postpartum hemorrhage can be prevented and health workers can prepare better for patients who had high risk of postpartum hemorrhage.

II. MATERIAL AND METHODS

This research is an analytical study with case series design conducted at RSUP Haji Adam Malik Medan, and Networking Hospital (RS USU, Sundari Hospital, and Pirngadi Hospital) starting from May to June 2022. Sampling was done by consecutive sampling technique. The research sample were maternity patients who met inclusion criteria, namely women with term pregnancy who gave birth spontaneously vaginally with cephalic presentation, and without assist delivery (vacuum extraction, fosceps); women who are willing to participate and are not included in exclusion criteria, namely women with history of uterine or amniotic infection in pregnancy, blood coagulation disorders, use of anti-coagulation, history of postpartum hemorrhage in previous pregnancies, preeclampsia or HELLP syndrome, history of uterine surgery; women with gemelli pregnancies, macrosomia, placenta previa,

placenta accreta, placental abruption; anemia in pregnancy and if postpartum hemorrhage occurs due to retained placenta, laceration of birth canal, and coagulation disorders.

Medial cubital vein blood as much as 5 cc was taken to assess calcium ion levels based on laboratory examinations at RSUP Haji Adam Malik Medan. Calcium ion levels will be divided into two, namely hypocalcemia if calcium ion level was below 4.6 mg/dL (1.16 mmol/L) and eucalcemia with calcium ion levels reaching 4.6-5.3 mg/dL (1.16-1.32 mmol/L). The bleeding volume was measured using a pictogram at time of vaginal delivery. Amount of postpartum blood loss is divided into two, namely below 250 mL and greater than 250 mL. Determination of this cut-off based on previous studies that determine mean value of postpartum blood loss volume.

Statistical Analysis

All data will be analyzed using statistical software and displayed in tabulated form. To analyze correlation between calcium levels and postpartum blood loss volume, a Chi Square test or other alternatives will be carried out when do not meet the requirements. The analysis results are said to be significant if $p < 0.05$ with 95% confidence interval

III. RESULTS

After conducting research from May-June 2022, 25 patients who gave birth met inclusion criteria and exclusion criteria. The results showed that majority of patients were 22 patients aged 21-35 years (88%), followed by 2 patients (8%) aged > 35 years and only 1 patient aged < 20 years (4%). Based on parity, 12 patients (48%) were primiparous, 9 patients (36%) were nulliparous, 3 patients (12%) and 1 patient (4%) were multiparous. According to antenatal care (ANC) visits, 11 patients (44%) had 4 times, 6 patients (24%) had 2 times, 5 patients (20%) had 3 times and 3 patients (12%) had 6 times ANC visits.

Table 1. Frequency Distribution of Research Sample Characteristics

Research Sample Characteristics		Total (n)	Percentage (%)
Age (years old)	≤ 20	1	4%
	21-35	22	88%
	≥35	2	8%
Parity	Nulliparous	9	36%
	Primiparous	12	48%
	Secundiparous	3	12%
	Multiparous	1	4%
Gestational age	38,7 + 0,502 weeks		
Antenatal care visits	2	6	24%
	3	5	20%
	4	11	44%
	6	3	12%
Calcium supplementation	Yes	0	0%
	No	25	100 %
UAC	< 23.5	5	20%
	> 23.5	20	80%
Postpartum Blood loss volume	<250	12	48%
	250-500	13	52%
Serum Calcium Levels	Hypocalcemia	23	92%
	Eucalcemia	1	4%
	Hypercalcemia	1	4%

If assessed by post-partum bleeding volume, 13 patients (52%) had blood loss volume 250-500 cc and 12 (48%) patients had <250 cc. In this research, all patients did not receive calcium supplementation. Based on Upper Arm Circumference (UAC), patients with UAC < 23.5 cm were 5 patients (20%), while patients with UAC > 23.5 cm were 20 patients (80%) while based on calcium ion levels, majority of 23 patients (92%) hypocalcemia. and 1 patient (4%) eucalcemia and hypercalcemia, respectively.

Table 2. Mean ± SD gestational age, bleeding volume and calcium levels

Research Sample Characteristics	Mean ± SD
Gestational Age	38,7 ± 0,502 minggu
Volume Blood Loss	256,01 ± 99,3 cc
Calcium ion levels	1,10 ± 0,098 mmol/L

Mean gestational age of research sample was 38.7 ± 0.502 weeks, with postpartum blood volume was 256.01 ± 99.3 cc and calcium ion levels was 1.10 ± 0.098 mm.

Table 3. The correlation of calcium ion levels and postpartum blood volume

	Variable	Spearman Test	
Blood loss volume	Correlation Coefficient	1.000	-.281
	Sig. (2-tailed)	.	.173
	N	25	25
Calcium	Correlation Coefficient	-.281	1.000
	Sig. (2-tailed)	.173	.
	N	25	25

Normality test with Saphiro Wilk (number of samples <50) showed that bleeding volume data was normally distributed (p>0.05) while calcium ion levels data were not normally distributed (p<0.05). Therefore, Spearman correlation test was conducted and found a weak negative correlation (r = -0.281) and not significant between two variables.

IV. DISCUSSION

Calcium is an important cofactor in coagulation cascade and hypocalcemia is independently associated with decreased optimal coagulation in vitro in bleeding patients. Recent studies in trauma victims have shown that hypocalcemia is associated with adverse outcomes. Several studies have shown that calcium plays a role in uterine contractions.[6] Uterine atony is major cause of obstetric bleeding. Low calcium levels reduce uterine muscle contractility and response to oxytocin.[14]

Electrical activity in uterine myocyte cells occurs due to depolarization and repolarization cycles that occur in uterine plasma membrane and this is called an action potential. Action potentials are mediated by several types of pathways, such as VGCC (Voltage Gated Calcium Channel), SOCE (store-operated calcium entry), ROCE (receptor-operated calcium entry), and/or via calcium storage in intracellular space. Uterine contractions can occur due to spontaneous activity in uterine smooth muscle caused by these action potentials and highly dependent on increase of calcium ions intracellular, contraction elements, and conduction system between uterine cells.[14]

Uterine smooth muscle stimulation is largely determined by movement of sodium (Na^+), calcium (Ca^{2+}) and chloride (Cl^-) ions into te cytoplasm and the movement of potassium (K^+) ions into extracellular space. Previously, these three ions were concentrated outside myometrium. The plasma membrane is usually more permeable to K^+ which in turn changes electrochemical gradient until an action potential occurs in myocytes. Furthermore, depolarization of plasma membrane opens VGCC (Voltage Gated Calcium Channel) or L-type Ca^2. Channels that result in entry of Ca^2 into the cell. Calcium ions then form complex bonds with calmodulin proteins and activate Myosin Light Chain Kinase (MLCK). MLCK must phosphorylate 20-kDa light chain of myosin, allowing interaction of myosin molecules with actin. The energy released from ATP by myosin ATPase results in crossbridge cycle between actin and myosin to produce contraction.[14]

In this research, majority of patients were aged 21-35 years (88%), primiparous (48%) and amount of antenatal care visits was 4 times (44%) with mean gestational age 38.7 $\pm$ 0.502 weeks. Abd El-Samie M et al study found mean age of patients experiencing postpartum hemorrhage was 28.75 $\pm$ 2.9 years old with parity 0-2 as much as 55% and parity > 3 as much as 15%. Post-partum blood loss volume in calcium intervention group was 677 $\pm$ 98.2 cc with 70% of patients requiring additional uterotonics and 100% of patients requiring blood transfusions. In Chong et al study, comparing metergin and calcium, mean blood loss was observed greater in calcium group compared to metergin group but the difference was not statistically significant.[15] The Epstein study also showed mean patients age was 29.5 (26.3-33.7) years old in mild postpartum hemorrhage group and 30.8 (28.2-35.1) years old in heavy postpartum hemorrhage group (> 500 cc). The number of parity found about 2-3 with gestational age at delivery was 39-40 weeks.[6] Wangwe et al also showed that majority of gestational age at delivery was >36 weeks (87.6%) with parity range 1-3 (66.8%).[16] The normal range of serum total calcium is 8.0 - 10.2 mg % or 2.2 - 2.5 mmol/L. About half of this total was ionized calcium (normal 4.0 - 4.6 mg% or 1.1 - 1.5 mmol/L). The mean patients age in Oguaka study was 29.36 ± 4.99 years old. The aged range of 25-29 years dominated with 57 patients (37.1%) while only 2 (1.4%) patients under 20 years old. Most of women were multiparous (58.6%); with 30.7% were primiparous and 10.7% were grandmultiparous.[7]

A total of 76 (54.3%) women in 39-40 weeks pregnancy; 45 (32.1%) women in 37-38 weeks pregnancy; while 19 (13.6%) women in 41-42 weeks pregnancy. Seventy (52.9%) women were eucalcemic; 65 (46.4%) women were hypocalcemic and only 1 (0.7%) women was hypercalcemic. Sixteen (11.4%) women experienced postpartum hemorrhage, while 124 (88.6%) did not experience postpartum hemorrhage. The prevalence rate of hypocalcemia in study population was relatively high, namely 46.43%. A prevalence rate higher than 80% has been reported for pregnant women in 37 and 41 weeks pregnancy, on Pakistan study.[7]

If assessed by postpartum blood loss volume, 13 patients (52%) had blood loss 250-500cc and 12 patients (48%) had blood loss <250 cc. If assessed based on UAC, as many as 5 patients (20%) had UAC <23.5 cm and 20 patients (80%) had UAC >23.5 cm (80%). According to Ministry of Health, pregnant women who at risk of Chronic Energy Deficiency (CED) are characterized by an upper arm circumference (UAC) < 23.5 cm. Pregnant women who experience CED are at high risk experiencing problems during pregnancy. Pregnant women with CED are at risk for complications such as anemia, bleeding, abnormal weight gain and are susceptible to infectious diseases. Malnutrition in pregnant women can also affect delivery process, namely prolonged labor, premature birth, postpartum hemorrhage and an increased incidence of surgical delivery.[17]

Based on ionic calcium levels, majority of 23 patients (92%) were hypocalcemic and 1 patient (4%) had eucalcemia and hypercalcemia, respectively. After Spearman correlation test was performed, it was found a weak negative correlation (r = -0.281) and not significant between calcium ion levels and postpartum blood volume. Research by Wangwe et al showed mean postpartum blood volume was 164.9 cc with 91.1% of patients had bleeding <499 cc and 8.9% of patients had bleeding > 500 cc.

In multivariable logistic regression model, fibrinogen and calcium concentrations were the only parameters that were independently associated with severity of postpartum hemorrhage with an odds ratio (OR) of 1.14 for each 10 mg/dl-1 decrease in fibrinogen (95%

CI, 1, 05-1.24; P=0.002) and 1.97 for each 0.1 mmol L-1 decrease in calcium (95% CI, 1.25-3.1; P=0.003). Normal calcium levels (1.16 mmol/L) had negative predictive value of 90.9% (95% CI, 87.5–93.7) for postpartum hemorrhage. Among patients at high risk for postpartum hemorrhage, low calcium at diagnosis of postpartum hemorrhage was associated with higher risk of massive bleeding independently of other laboratory and clinical indicators.[6]

Wang et al have reported that women who have low serum calcium levels have higher risk of postpartum hemorrhage than women who have normal calcium levels within 2 hours postpartum, and normal serum calcium prevents postpartum hemorrhage due to uterine atony. Postpartum bleeding was higher when antepartum serum calcium was 1.05 mmol/L.[7]

According to Qin et al study, mean ionized calcium of participants with primary postpartum hemorrhage from uterine atony (1.0±0.35 mmol/L) in Oguaka study was lower than critical value.[7] Calcium plays an important role in coagulation cascade, platelet aggregation, regulation of vasomotor tone, and cardiac function. Calcium testing is widely available in most emergency departments, operating theatres, and ICUs as a feature of most blood gas analysis laboratories. Other mechanisms involved increased sympathetic activity, altered sensitivity and impaired parathyroid function, end-organ resistance to parathyroid hormone, altered synthesis and vitamin D action, all of which are induced by pro-inflammatory cytokines. Studies in healthy volunteers have shown that calcium levels >0.56 mmol/L are unlikely to cause significant coagulation abnormalities in vitro. In vitro studies, normocalcemia was associated with oxytocin-induced contractility produced by hypothalamus, compared with contractions produced by oxytocin in uterine tissue with abnormal calcium. Recent studies have shown that higher doses of calcium chloride (1 g) reduce uterine atony incidence in high-risk patients. Calcium levels found in uterine tone can be an additional therapeutic targets in postpartum hemorrhage management.[6] In some studies, decrease in maternal calcium concentration has been observed with increasing gestational age, during pregnancy where calcium concentration in mother's body is slightly lower than calcium in umbilical cord blood. Changes in woman's body metabolism during pregnancy, which are designed to compensate increased calcium requirements of mother and fetus could explained no significant difference between maternal and fetal serum calcium concentrations. Pregnancy is associated with increase of estrogen and progesterone serum concentrations in woman's body, which subsequently affects many substances concentration, including calcium. Decreased urinary calcium excretion and intense bone remineralization are observed during pregnancy.

In addition, increased synthesis of 1,25-dihydroxyvitamin D enhances intestinal calcium absorption and its storage in maternal skeleton, to supply fetus with sufficient calcium later in life. Pregnant women age can affect mineral status, especially calcium levels.[18] WHO recommends calcium supplements for pregnant woman with daily dose (1.5-2 g) divided into two or three dose. In Ajong et al's study, calcium levels in pregnant women who consumed more than 4 months supplementation were higher than women who consumed less than 3 months, although not statistically significant (p = 0.335).[19]

Optimal serum calcium levels are essential for effective uterine contractions and low serum calcium levels can cause uterine atony and varying degrees of postpartum haemorrhage. Patients with serum calcium levels < 8 mg tend to experience uterine atony and postpartum hemorrhage.[8] Sheema suggests that all delivery patients should done serum calcium levels evaluation and if serum calcium is < 8.5 mg/dl, postpartum hemorrhage should be anticipated. In these patients, it is recommended to give calcium gluconate intravenously in second stage of labor in cases of vaginal delivery or before cesarean section with lower uterine segment incision, to prevent postpartum hemorrhage and aggressive management such as hysterectomy, reduce maternal morbidity and mortality. Calcium shows its effect by activating muscle proteins and produce effective uterine contractions. Intravenous administration of calcium gluconate can increase uterine contractions which play a role in prevention and reduced postpartum bleeding by increasing uterine tone. Patients with postpartum hemorrhage caused by uterine atony who do not respond to oxytocin usually respond well to intravenous calcium gluconate, which is characterized by increased uterine tone.[20]

V. CONCLUSION

Weak negative correlation (r = -0.281) but not significant was found between calcium ion levels and postpartum blood volume.

VI. ACKNOWLEDGMENT

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