SERUM CALCIUM AND MAGNESIUM LEVELS RATIO IN PATIENTS WITH AND WITHOUT HYPOTONIC UTERINE INERTIA

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ABSTRACT

Hypotonic uterine inertia is defined as contractions of uterine when an active phase of labor begins, measured less than 180 Montevideo units beyond the expected time of labor. Another contributing factor to its mechanism is the imbalance of the extracellular calcium level.When extracellular calcium level is inadequate, the myometrium response to oxytocin decreases and the calcium influx inter-cell membranes are suppressed, thus inhibit uterine contractions. Magnesium can also inhibit intracellular and/or extracellular muscle contractions by restricting the calcium intake freely accessible on extracellular; hindering the channel-dependent influx on the extracellular calcium, as well as competing with calcium on sarcoplasmic reticulum that leads to the decrease in the level of calcium used during interactions of actin, myosin and myometrium repolarization. This is a comparative analytical study with cross sectional design, examining the level of calcium and magnesium of the serum in normal deliveries and in those with hypotonic uterine inertia. The normal group consists of 57 patients, and 63 patients with hypotonic uterine inertia who were treated in RSUP Dr. Hasan Sadikin and its satellite hospitals from March to September 2014 and met the inclusion criteria. The level of calcium was measured using ion-selective electrode technique while the optical photometry method was used to measure the level of magnesium.The ratio value of calcium and magnesium level in labor with hypotonic uterine inertia is 4.45. The cut-off value of the predictor point for hypotonic uterine inertia is a calcium channel $\leq$ 8.5 mg/dl, increasing the chance for hypotonic uterine inertia by 4.17% . With the magnesium level > 1.84mg/dl, the risk for uterine inertia increases by 2.90%. We draw conclusions that the calcium level in labor with hypotonic uterine inertia is lower than in normal labor whereas the magnesium level in labor with hypotonic uterine inertia is

higher. There is a significant correlation between low calcium level and high level of magnesium in for hypotonic uterine inertia.

Keywords: Calcium, Hypotonic uterine inertia, Magnesium

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INTRODUCTION

Hypotonic uterine inertia remains an issue in the field of obstetrics. The annual report of Obstetrics and Gynecology Department in Hasan Sadikin Hospital by the year of 2012 showed 1,468 cases of caesarean section from 2,947 deliveries (49%). The rate of caesarean section due to failures of oxytocin augmentation in hypotonic uterine inertia was the most significant indication for cesarean sections.[1] Hypotonic uterine inertia is defined as uterine contractions with less than 180 Montevideo units that usually occur when labor has entered the active phase, i.e. when the opening of the cervix has reached 3 or 4 cm and beyond the expected time limit.[2] The etiology of uterine inertia is still unknown, even though several factors have been recognised such as primigravida especially in old age, hormonal influences due to lack of prostaglandin or oxytocin and an inaccurate analgesic usage. Some influence of local factors are overdistention of the uterus, developmental anomalies such as hypoplastic uterus, uterine myoma, malpresentation, malposition, cephalopelvic disproportion and chorioamnionitis.[3-5]

The elongation of labor active phase involves a complex interaction between the strength of uterine contractions (power factor), fetus condition (passanger factor) and the condition of the birth canal (passage factor). In the early phase of labor, oxytocin activates phospholipase C-inositol pathway, increases intracellular calcium levels and stimulates smooth muscle contraction of the myometrium. The contributing factors to hypotonic uterine inertia generally work through the mechanism of serum calcium disorders. If the extracellular calcium is not enough, the myometrium cells' response to oxytocin decreases.[2,3]

Magnesium can also inhibit intracellular and extracellular muscle contractility. In this mechanism, magnesium inhibits free extracellular calcium intake and channel-dependent influx of the extracellular calcium. Magnesium also competes with calcium in the sarcoplasmic reticulum which will decrease the calcium levels that will be used in the interactions between actin-myosin and myometrium repolarization. High extracellular magnesium concentration will also increase free intracellular magnesium concentration that subsequently leads to suppression of calcium influx across the cell membrane and inhibits the uterine contraction. The higher the levels of magnesium, the higher the levels of calcium required to prevent potential effects. [2,4,6,7]

METHODS

This study used a cross-sectional method to determine the correlation ratio of calcium and magnesium levels in patients experiencing hypotonic uterine inertia during labor. The subjects include patients admitted into the emergency department and maternity wards of the Hasan Sadikin and its network hospitals during the study period. These patients entered active phase of labor, both without and with hypotonic uterine inertia (expressed by cardiotocography examination). All subjects were volunteers and they filled out an informed consent.

The inclusion criteria include primigravida, 37-42 weeks of gestational age, single pregnancy, intact membrane and location of fetus head, and parturients in the active phase of the first stage. Exclusion criteria include labor with magnesium sulfate therapy, thyroid disorder, primary infertility, conditions in which the levels of calcium and magnesium cannot be performed, and blood samples damage.

Eta test was used to analyze the correlation of serum calcium and magnesium levels ratio in both groups.The entire calculation was completed using SPSS/PC + version 13.0. Significance levels was determined when the value of calculated F>table F.

RESULTS

This research was performed on patients who came to emergency department of Hasan Sadikin hospital and its networks during the period of March 2014 until September 2014, who met the inclusion criteria. This study consisted of two groups, 63 subjects entering the

active phase and experiencing uterine inertia and 57 who had normal deliveries as control group. Characteristics of the subjects are shown in Table 1.

Table 1. Characteristics of the Subjects

Characteristics	Patients with Hypotonic Uterine Inertia (n = 63)	Patients without Hypotonic Uterine Inertia (n = 57)	P value
Maternal age			0.872
< 25 years old	12 (19%)	18 (31.6%)	
25-29 years old	21 (33.3%)	18 (31.6%)	
30-34 yearsold	24 (38.1%)	12 (21.1%)	
>35 years old	6 (9.5%)	9 (15.8%)	
X (SD)	27.8 (5.4)	28.5 (6.5)	
Median	25.00	28.00	
Range	20-43	18-41	
Parity			0.724
0	24 (38.1%)	15 (26.3%)	
1-2	27 (42.9%)	30 (52.6%)	
3-4	12 (19.0%)	12 (21.1%)	
Gestational age			0.681
< 38 weeks	21 (33.3%)	12 (21.1%)	
38-40 weeks	30 (47.6%)	33 (57.9%)	
≥ 40 weeks	12 (19.0)	12 (21.1%)	
X (SD)	38.24 (1.37)	38.42 (1.17)	
Median	38.00	38.00	
Range	36-41	37-41	
Infants weight			0.282
X (SD)	3,000 (176. 1)	2,957.9 (219.4)	
Median	3,000	2,900	
Range	2,600-3,300	2,700-3,400	

*Statistical analysis was based on Chi Square test; only maternal age analysis used Mann-Whitney test.

Based on the two tests performed, Chi Square to analyze the characteristics of parity, gestational age and infant weight; and Mann-Whitney test to analyze the characteristics of maternal age, the p values for maternal age, parity, gestational age, and infants weight are 0.87, 0.724, 0.681, and 0.282 respectively. Characteristics of respondents are not statistically significant, however, the data is homogeneous and valuable to be compared.

Table 2. Comparison of Serum Calcium and Magnesium Levels in Patients with and without Hypotonic Uterine Inertia

	Patients with Hypotonic Uterine Inertia (n = 63)	Patients without Hypotonic Uterine Inertia (n = 57)	P value
Calcium levels (mg/dL)			< 0.001
X (SD)	8.49 (0.37)	9.00 (0.33)	
Median	8.4	8.9	
Range	7.8-9.7	8.6–9.8	
Magnesium levels (mg/dL)			< 0.001
X (SD)	1.98 (0.44)	1.60 (0.14)	
Median	1.85	1.58	
Range	1.51–2.95	1.31–1.84	

*Based on Mann-Whitney test

Shown on Table 2, the comparison between calcium levels in patients with and without hypotonic uterine inertia with the P value<0.001, and on the comparison between magnesium levels in patients with and without hypotonic uterine inertia with theP value <0.001.

Table 3. Comparison of Calcium and Magnesium Levels Ratio in Patients with and without Hypotonic Uterine Inertia

Calcium/ Magnesium Levels Ratio	Patients with Hypotonic Uterine Inertia (n = 63)	Patients without Hypotonic Uterine Inertia (n = 57)
X (SD)	4.45 (0.81)	5.65 (0.54)
Range	2.96–5.58	4.89–6.87

* t = 5.511 ; P ≤ 0.001

Shown on Table3 the mean ratio of calcium/ magnesium levels in patients with hypotonic uterine inertia is 4.45 with a range of 2.96-5.58, whereas the mean ratio of calcium/ magnesium levels in patients without hypotonic uterine inertia is 5.65 with a range of 4.89-6.87.

Table 4. Cut off Point for Calcium and Magnesium Levels as a Predictor of the Occurrence of Hypotonic Uterine Inertia

Cut Off Point	Hypotonic Uterine Inertia	Without Hypotonic Uterine Inertia	Sensitivity (%)	Specificity (%)	Accuracy (%)	P value
Calcium Levels (mg/dL)			71.4	100	85	<0.001
≤ 8.5	45	0				
≥ 8.5	18	57				
	RP (CI 95%) : 4.17 (2.07–8.371)					
Magnesium Levels (mg/dL)			52.4	100	75	<0.001
≥ 1.84	33	0				
≤ 1.84	30	57				
	RP (CI 95%) : 2.90 (1.76–4.79)					

* RP: Risk Prevalence; CI: Confidence Interval

Table 4 shows that inpatients withserum calcium levels ≤ 8.5 mg/ dL, the risk of hypotonic uterine inertia in labor is 4.17 times higher than those with serum calcium levels > 8.5 mg/ dL. The accuracy of the maternal calcium levels to predict the occurrence of hypotonic uterine inertia in a labor is 85%, 71.4%,and 100% respectively. It is shown that if the levels of the maternal serum magnesium > 1.84 mg / dL, the risk of hypotonic uterine inertia in labor is 2.90 times higher than those with serum magnesium levels ≤ 1.84 mg/ dL. The accuracy of the maternal magnesium levels to predict the occurrence of hypotonic uterine inertia in a labor is 75%, 52.4%, and 100% respectively.

DISCUSSION

In this study the characteristics of the subjects consist of maternal age, parity, gestational age, and infants weight (Table 1). These characteristics were selected due to their potential confounding variables that may affect the validity of this study. In both study groups, no significant differences are found in terms of maternal age, parity, gestational age and infants weight, thus, these results are valuable as a comparison for further study.

Calcium and Magnesium Levels in Patients with and without Hypotonic Uterine Inertia

Based on the results shown in Table 2 using unpaired statistical t test and p value of <0.001 or significant, this study confirmed that patients with hypotonic uterine inertia have low levels of calcium compared with those with normal deliveries. The levels of serum magnesium are found higher in patients with hypotonic uterine inertia.

Relationship Between Calcium and Magnesium Levels and the Incidence of HypotonicUterine Inertia

Based on data shown in Table 2, the mean serum calcium level among patients with hypotonic uterine inertia is 8.49 (0.37) with the median value of 8.4 and a range of calcium levels between 7.8 to 9.7; whereas the mean serum calcium levels among patients without hypotonic uterine inertia is 9.00 (0.33). This data represents the mean serum calcium levels in patients without hypotonic uterine inertia which is higher than in those with hypotonic uterine inertia. Similarly, the median value of serum calcium levels in patients without hypotonic uterine inertia is higher than in those with hypotonic uterine inertia. The lowest of serum calcium level in patients with hypotonic uterine inertia is 7.8 and the highest is 9.7, whereas

the lowest of serum calcium levelin patients without hypotonic uterine inertia is 8.6 and the highest is 9.8.

The determinant value of calcium levels (cut-off point) resulting from receiver operating characteristic (ROC) is significant with a significance value of p = 0.001 (Fig.1), hence, the determinant value ≤ 8.5 mg/ dL can be used as a guidance to predict the occurrence of hypotonic uterine inertia during labor with 4.17 times higher risk in patients with calcium levels ≤ 8.5 mg/ dL. This result is consistent with the previous studies conducted by Formin VP *et al.* (2006) that maternal serum calcium levels increase the risk of hypotonic uterine inertia.[8]

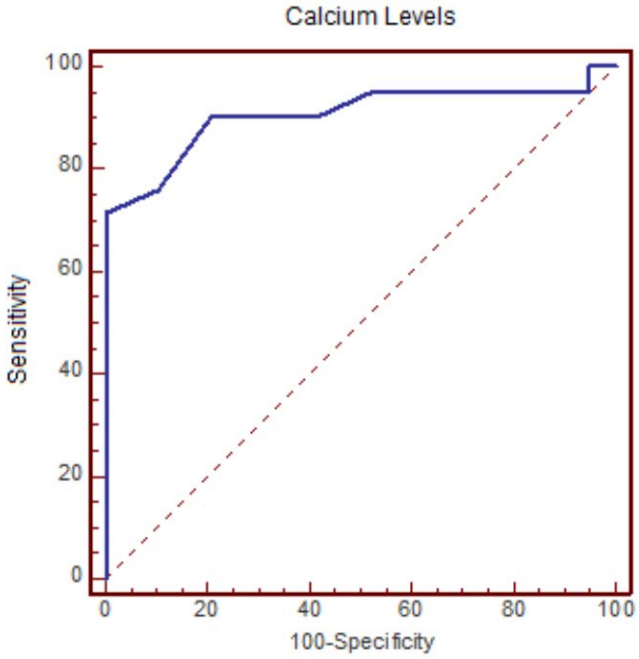

Figure 1. ROC of Calcium Levels in Patients with Hypotonic Uterine Inertia.

The determinant value of magnesium levels (cut-off point) resulting from ROC curve is significant with a significance value of p = 0.001 (Fig.2), hence, the determinant value> 1.84 can be used as a guidance to predict the occurrence of hypotonic uterine inertia during labor, with a risk of 2.90 times in patients with magnesium levels> 1.84 mg/ dL.

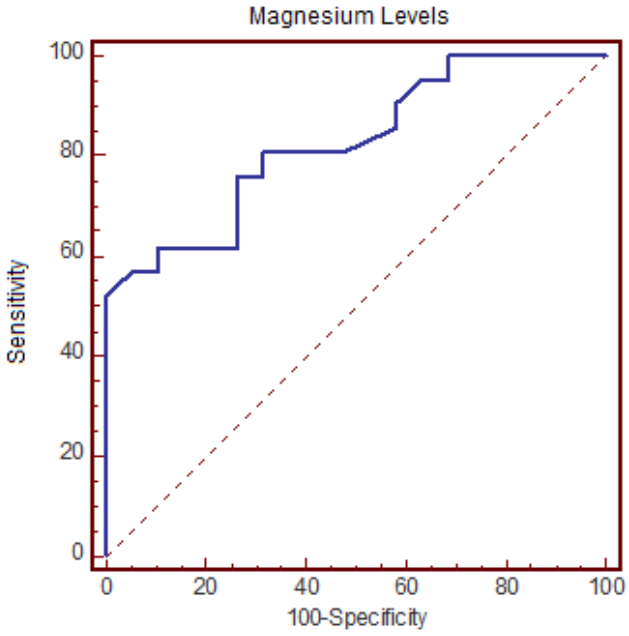

Figure 2. ROC of Magnesium Levels.

In 1984, Robalo and Noakes showed that on animal experiment drug induced hypocalcemia during labor, and it could provoke a poor uterine contractility. This kind of experiments are not acceptable on human due to moral issues.[9] Calcium is widely used in human metabolism and normal function, so that a total serum calcium level is important to be noticed on every laboring patient. We can estimate a patient's body functions regarding it's total calcium serum level, since serum calcium level is closely related to homeostasis and muscles
contractility.[10-12]

Calcium is needed for muscles' contraction. In this study, we shows that the calcium level in labor with hypotonic uterine inertia is lower than in normal labor. Wattimury *et al*. (2013) also showed that total serum level of calcium and ion calcium in hypotonic uterine inertia is lower than the level of which in normal labor.[13] The strength of smooth muscles' contraction extremely depends on the level of extracellular calcium.[14,15] It has been proved on animal studies that uterine contraction in mammals can be restricted by giving some drugs which decrease serum calcium level.[16-18]

This study shows that the magnesium level in labor with hypotonic uterine inertia is higher than in normal labor. In the process of muscles' contractility, magnesium inhibits the muscles' contraction. Magnesium inhibits free extracelullar calcium intake and extracellular calcium channel-dependent influx. It also competes with calcium in sarcoplasmic reticulum

that leads to the decrease of calcium level used in actin-myosin interaction and myometrium repolarization. The high level of extracelullar magnesium may lead to the increased level of free intracellular magnesium. It will subsequently lead to calcium supression and influx among cell membrane due to oxytocin induction, which finally inhibit the uterine contraction. Magnesium also prevents agonist stimulation in releasing intracellular calcium through inositol 1,4,5-trisphosphate receptor, and blocks calcium attachment in the specific site intracellularly.[19-21]

CONCLUSION

The serum calcium level in patients with hypotonic uterine inertia is lower than in those without hypotonic uterine inertia, whereas the serum magnesium level in patients with hypotonic uterine inertia is equal or higher than in those without hypotonic uterine inertia. There is a strong correlation between the ratio of low serum calcium and high serum magnesium levelsin patients with hypotonic uterine inertia. The incidence of hypotonic uterine inertia in labor can be predicted by the cut-off value of calcium and magnesium levels.

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