Original Article

The Role Of Serum Electrolytes In Pregnancy Induced hypertension

Biochemistry Section

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ABSTRACT

Background and Objectives: Pregnancy Induced Hypertension (PIH) is one of the most common complications of pregnancy and it contributes significantly to the maternal mortality, premature birth, intra uterine growth retardation (IUGR) and perinatal mortality. The study of electrolytes is gaining ground in the pathophysiology of hypertension. Multiple strategies have been proposed and evaluated for the prevention and management of PIH, which include the moderate dietary restriction of sodium and the administration of magnesium and calcium. **Methods:** Our study consisted of 50 normal non-pregnant women, 50 normal primigravida in the second or third trimester of pregnancy and 50 pregnant women with PIH. The present study was undertaken to evaluate the serum ionized calcium, magnesium, sodium and potassium levels in PIH and to find out if the deficiency of these electrolytes was a predisposing factor in the genesis of PIH. **Results:** There was a linear fall in serum ionized calcium, magnesium and sodium levels in the normal pregnancy cases as compared to those in the non-pregnant controls (P< 0.001), with a further significant fall in the PIH cases as compared to the normal pregnancy cases (P< 0.0001). There was no significant change in the potassium levels in the PIH cases as compared to those in the normal pregnancy cases (P<0.457). A decreased calcium intake leads to an increase in the parathyroid hormone, which increases intracellular calcium, thus leading to an increase in the vascular smooth muscle contraction and thus, an elevation in the blood pressure. Low levels of magnesium and sodium cause hypocalcaemia, which in turn increases the blood pressure. Thus, along with a moderate dietary restriction of sodium, a dietary supplementation of calcium and magnesium in the form of milk, cheese, soybean products, leafy vegetables, etc. during pregnancy, could result in a reduction in the incidence of PIH.

Key Words: Calcium, Electrolytes, Magnesium, PIH, Sodium

INTRODUCTION

Hypertension is a universal problem and it complicates at least 10% of all the pregnancies. It is a well known fact that electrolytes play an important role in the aetiopathogenesis of hypertension. Dietary sodium restriction is one of the prime treatments of high blood pressure. Preeclampsia (hypertension in pregnancy in association with the excretion of > 300 mg of urinary protein per day after 20 weeks of gestation) is an important cause of both perinatal and maternal morbidity and mortality.

Calcium plays a critical role in the function of the cardiac and vascular smooth muscles. It is known that the deficiency of calcium may lead to irritable nervous muscular symptoms, even tetanic convulsions, bleeding diathesis, capillary haemorrhages, tissue exudation and osteomalacia. These features have got some resemblance to the clinical manifestations and pathological findings in pregnancy induced hypertension (PIH), particularly eclampsia. Increase in the intracellular calcium causes vasoconstriction, increase in the peripheral resistance and therefore, an increase in the blood pressure [1]. Magnesium modulates the cardiovascular effect of sodium and potassium and it is the co-factor for the sodium-potassium ATPase activity [2]. Since the electrolytes: calcium, magnesium, sodium and potassium contribute significantly in the functioning of the vascular smooth muscles, the present study was designed to evaluate the role of these electrolytes in the genesis of PIH.

MATERIAL AND METHODS

The Ethical and Research Committee of the Medical College and Hospital approved the study protocol and informed consent was obtained from the controls and the patients before the collection of the blood samples. The study included 50 normal, healthy, non-pregnant women in the age group of 20-40 yrs as the controls, 50 cases of healthy primigravida of the same age receiving antepartum care at the outpatients department and 50 cases of pregnant women with PIH who were admitted to the Dept. of Obstetrics and Gynaecology, District Hospital. All cases were selected by taking a detailed medical history and by physical examination.

INCLUSION CRITERIA

Patients with an onset of hypertension i.e. more than 140/90 mmHg during the second or third trimester of pregnancy,

- Excretion of more than 300 mg of urinary Protein per 24 hrs,
- oedema,
- Patients with or without convulsions and
- sudden weight gain.

EXCLUSION CRITERIA:

Patients suffering from

- Diabetes mellitus,
- Nephritis or
- Any other systemic disease.

About 2ml of venous blood was collected from the antecubital vein by taking aseptic precautions. Care was taken to prevent venous stasis during the sample collection. The blood was allowed to clot and the serum was separated by centrifugation. The estimation of the parameters was carried out within 4-6 hrs. The samples were analysed for serum total calcium by the O-Cresolphthalein complexone method [3], for serum ionized calcium by ion selective

electrode method [4], for serum magnesium by the calmagite dye method [5] and for serum sodium and potassium by the flame photometer method (Systronics). The internal control sera of two different levels were used to calibrate the instruments.

The normal values of different parameters under standard conditions are:

- Serum Total calcium 9-11mg/dl,
- Serum ionized calcium 4.5-5.5mg/dl,
- Serum magnesium 1.8-3 mg/dl,
- Serum sodium 135-145meq/L and
- Serum potassium 3.5-5 meq/L.

One way ANOVA, followed by the Bonferroni multiple comparison test, was employed for the statistical analysis of the data to compare the groups.

RESULTS

The age of the PIH patients was 25.6± 3.46 (range 20-29) years. A majority (51.3%) of the patients were in the age group of 21 to 25 years. Of the 50 PIH patients, 34 were primigravida (68%) and 16 were multigravida (32%). On an average, preeclampsia was noted at 33.73 ± 5.91 gestational weeks. The results of various biochemical parameters in normal, non-pregnant, normal primigravida cases and in PIH cases, along with age and body mass index (BMI) are shown in [Table/Fig 1].

Parameters	Control (n=50)	Normal Primigravida (n=50)	PIH (n=50)
Age(Yrs)	23.1±2.78	24.3±2.67	25.6±3.467
BMI(kg/m^2)	22.87±1.74	25.82±2.56	26.93±3.78
Total Calcium(mg/dl)	10.41±0.50	9.21±0.61*	8.49±0.71*#
Ionized Calcium (mg/dl)	4.85±0.31	4.02±0.54*	3.43±0.52*#
Magnesium (mg/dl)	2.63±0.22	1.84±0.16*	1.35±0.17*#
Sodium(meq/L)	143.08±2.83	135.44±3.38*	130.84±3.03*#
Potassium (meq/L)	4.51±0.34	3.62±0.28*	3.57±0.27*

[Table/Fig 1]: Serum levels of total Calcium, ionized calcium, magnesiam, sodium and Potassium in non-pregnant (Controls), normal primigravida and Pregnancy with PIH.

Values are expressed as mean+SD;
n-indicates number of study population,
* statically significant change(p<0.001) Vs Control group,
#statically significant change(p<0.001)Vs normal primigravida group

Serum total calcium, ionized calcium and magnesium levels were significantly decreased in the normal primigravida cases as compared to those in the non-pregnant healthy controls (p<0.001). Further, a highly significant decrease was observed in the PIH cases as compared to the normal primigravida cases (p<0. 001).

It was observed that serum sodium and potassium levels were decreased significantly in the normal primigravida cases as compared to those in the non-pregnant controls (p<0. 001). Serum sodium levels were further decreased significantly in the PIH cases as compared to those in the normal pregnancy cases (p<0.001), but there was no significant change in the serum potassium levels(p<0.457).

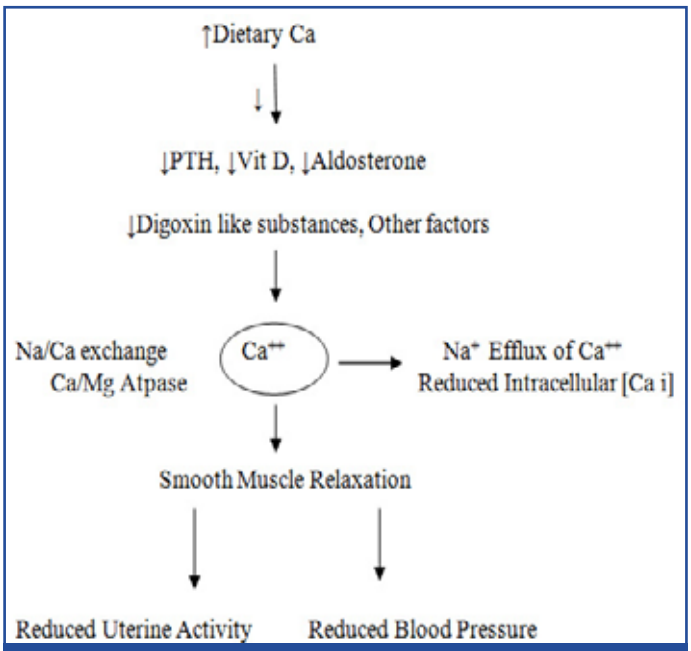
DISCUSSION

The estimation of serum electrolytes in PIH provides a very useful index for the study of physiological and pathological changes during pregnancy. In the present study, a significant decrease in serum total and ionized calcium levels was seen in the normal primigravida cases as compared to the non-pregnant controls, with a further highly significant decrease in the PIH cases as compared to the normal pregnancy cases. This indicates an association between calcium deficiency and PIH. This contention is amply supported by a few other studies [6],[7]. Seely E W et al confirmed that preeclamptic women had lower serum ionized calcium levels than normotensive, third trimester, pregnant women (1.20 +/- 0.01 vs. 1.26 +/- 0.01 mmol/L, P less than 0.02). They also found that preeclamptic and normotensive pregnant women had equivalent levels of 25-hydroxyvitamin D [25(OH)D]; however, preeclamptics had significantly lower 1,25-dihydroxyvitamin D [1,25-(OH)2D] levels (172.1 +/- 18.5 vs. 219.6 +/- 12.7 pmol/L, P less than 0.05). Thus, lower 1,25-(OH)2D levels may contribute to the suboptimal intestinal absorption of calcium during a time of increased calcium demand, thus resulting in lower ionized calcium levels, increased PTH, and hypocalciuria in preeclampsia. Abnormalities in calcium homeostasis may contribute to the increased vascular sensitivity which is documented in preeclampsia [8]. Calcium metabolism is under strain during pregnancy. Expectant mothers need to store about 30-50 gm of calcium during the course of pregnancy, of which 25gms are needed by the foetus. Eighty percent of the total foetal calcium is deposited during the third trimester. The transport of ionized calcium from the mother to the foetus increases from about 50 mg/day at 20 weeks of gestation to a maximum of about 350 mg/day at 35 weeks of gestation [9]. Decreased serum calcium levels lead to an increase in the parathyroid hormone levels, thereby increasing the intracellular calcium levels, which leads to an increase in the vascular smooth muscle contraction and thus, an increase in the blood pressure. Despite the low circulating calcium levels, the intracellular level of calcium ions is high, which leads to hypertension [1]. Some researchers [10] have also shown an increased, intracellular, ionised calcium concentration and an increased sensitivity of these cells to angiotensin II in women with preeclampsia. Belizan hypothesized that a low calcium intake results in high parathyroid hormone levels and increased membrane permeability. As a result, calcium is released from the mitochondria and it enters the cytoplasm, thus resulting in increased intracellular free calcium levels and decreased serum calcium levels. The elevation of cytoplasmic calcium levels triggers smooth muscle contraction, thus resulting in vascular constriction and increased blood pressure [1].

Several studies have examined the effects of calcium supplementation on blood pressure during pregnancy, thus investigating the role of calcium supplementation and its effects on blood pressure. [11],[12] There has been a near-unanimity in the observed phenomenon that calcium supplementation of approximately 2 g of elemental calcium (5 g calcium carbonate) per day, results in an overall lowering of blood pressure and an overall reduction in the incidence of the hypertensive disorders of pregnancy. The mechanism is the same as that for blood pressure reduction, that is, an overall shift of intracellular ionized calcium to the extracellular space, resulting in smooth muscle relaxation.

Bucher HC [13] et al conducted a meta-analysis of randomized controlled trials on the effect of calcium supplementation on pregnancy-induced hypertension and preeclampsia. The pooled analysis showed a reduction in systolic blood pressure of -5.40 mm Hg (95% confidence interval [CI], -7.81 to -3.00 mm Hg; P<.001) and in diastolic blood pressure of -3.44 mm Hg (95% CI, -5.20 to -1.68 mm Hg; P<.001). The odds ratio for preeclampsia in women with calcium supplementation compared with placebo was 0.38 (95% CI, 0.22 to 0.65). Hence, they concluded that calcium

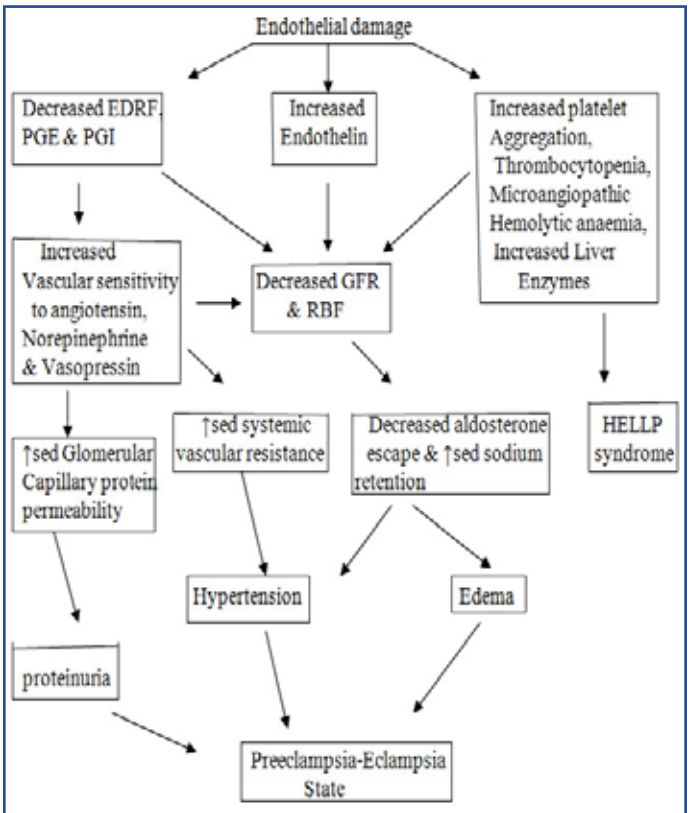
supplementation during pregnancy leads to an important reduction in systolic and diastolic blood pressure and preeclampsia.



[Table/Fig: 2] shows the proposed mechanism whereby calcium supplementation may reduce blood pressure [14].

There was a significant decrease in the serum magnesium levels in the normal pregnancy cases as compared to those in the non-pregnant controls and this significantly decreased further in PIH. Our findings are consistent with the reports of some researchers, [15],[16]. Magnesium affects the cardiac and smooth muscle cells by altering the transport of calcium and its binding to the membrane and organ cells. Magnesium acts peripherally to produce peripheral vasodilatation and a fall in blood pressure. Thus, low levels of magnesium predispose to an increase in the arterial pressure [17]. Magnesium is known to increase the prostacycline release from the endothelial cells of the blood vessels, which acts as a potent vasodilator. In addition, magnesium depletion increases the vasoconstrictor effect of angiotensin II and nor-adrenaline. Magnesium also has a substantial beneficial effect in preeclampsia for the prevention and treatment of convulsions. Therapeutic magnesium sulphate which is used in PIH inhibits phosphatidyl inositol-4, 5-bisphosphate specific phospholipase C activity and subsequent calcium release in the cells, thus leading to decreased intracellular calcium levels and a decrease in blood pressure [18]. Hypomagnesaemia and a negative magnesium balance have been found in primary aldosteronism. Aldosterone increases the urinary excretion of magnesium. PIH has been shown to have secondary aldosteronism. The tendency of the depletion of magnesium might be because of the aldosterone effect.

We also found the serum sodium levels to be significantly decreased in the PIH cases as compared to that in the non-pregnant controls and in the normal primigravida. Our findings are in accordance with those reported by other authors, [19],[20]. Sodium transport is altered across the cell membrane and this leads to the accumulation of sodium in the extravascular spaces and a decrease in the plasma sodium levels. The serum sodium levels tend to decline in cases of preeclampsia as the disorder increases in severity [19]. The intrarenal production of cyclic GMP, endothelin and PGE2 are all decreased in preeclampsia and this may have implications in the sodium retention, hypertension, intrarenal thrombosis and the vasospasm of preeclamptic pregnancy [21]. One proposal which was derived from a number of experimental evidences, suggests that an excessive intake of sodium chloride leads to sodium and water retention, the expansion of ECF and intravascular volume, increased venous return and an elevated cardiac index. As elevated blood flow to the tissue continues, whole body autoregulation takes place, with a subsequent increase in the total peripheral resistance and the eventual development of hypertension [22]. The "peripheral arterial vasodilation hypothesis" of sodium and water retention in pregnancy and its implications for the pathogenesis of preeclampsia-eclampsia explain that with increased endothelial damage, sodium retention and increased sensitivity to angiotensin lead to hypertension, oedema and proteinuria, the diagnostic triad of preeclampsia-eclampsia [23] [Table/Fig 2,3].



[Table/Fig: 3] shows that endothelial damage attenuates the vasodilation of pregnancy and leads to pathophysiologic events that characterize preeclampsia-eclampsia [23].EDRF= endothelial-derived relaxing factor; PG=Prostaglandin; GFR= Glomerular filteration rate; RBF= Renal blood flow; HELLP= hemolysis, elevated liver enzymes, low platelets

Though there was a decrease in the potassium levels in the normal pregnancy cases and PIH as compared to the controls, there was no significant difference in the potassium levels in PIH as compared to those in the normal primigravida. In erythrocytes, the extrusion of the cellular sodium load is accomplished by the Na/K pump and by the Na/K co-transport. An abnormal low rate of net sodium extrusion by the Na/K co-transport was observed in the PIH patients. PIH may be an early sign of abnormality in the transport of sodium and potassium across the vascular smooth-muscle cell membrane, which is responsible for the maintenance of blood pressure [24],[25].

CONCLUSION

From the above study, though calcium and magnesium deficiencies cannot be pin pointed as the sole factors for the aetiology of PIH,

their relationship with PIH cannot be denied. Both magnesium and sodium are known to decrease the intracellular calcium by different mechanisms, thus leading to smooth muscle contraction and an elevation in blood pressure. The recommended daily allowance of calcium for a pregnant woman is 1200 mg. One cup of yogurt provides the same amount of calcium as one cup of milk (302 mg). Other dairy products providing a significant amount of calcium include Swiss cheese (260 mg per ounce), jack cheese (210 mg per ounce), cottage cheese (115 mg per ½ cup), and ice cream (176 mg per cup). Non-dairy foods which contain calcium include collard leaves (270 mg per ¾ cup), broccoli (160 mg per stalk), okra (150 mg per cup), and acorn squash (108 mg per cup). Thus, along with a dietary restriction of sodium, a dietary supplementation of calcium and magnesium in the form of milk, cheese, soybean products, leafy vegetables, etc. during pregnancy, could result in a reduction in the incidence of PIH.

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