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Original Research Article

Comparison of high dose calcium and vitamin D3 versus low dose aspirin combined with high dose calcium and vitamin D3 in prevention of preeclampsia: a prospective comparative study

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ABSTRACT

Background: It is hypothesized that, vitamin D supplementation with or without calcium in pregnancy has important role in reducing risk of preeclampsia. This study was designed to compare the efficacy of high dose calcium, vitamin D3 supplementation with high dose calcium, vitamin D3 combined with low dose aspirin, in prevention of preeclampsia.

Methods: This hospital based prospective comparative study was conducted in the Department of Obstetrics and Gynaecology, Koppal Institute of Medical Sciences, Koppal, Karnataka State, India. A total of 210 females with gestational age of 12 weeks attending antenatal check-up divided into three groups of 70 each as group A (calcium and vitamin D3), group B (calcium and vitamin D and aspirin) and group C (routine antenatal medications) were enrolled.

Results: Most of the women in all the three groups were aged between 21 to 25 years ($p=0.913$). Gestational age of 12 weeks at the start of supplementation was noted in 58.57%, 64.29% and 41.43% of the women in group A, B and C had respectively ($p=0.031$). Majority of the women (88.33%) of the women in group C had pedal oedema ($p<0.001$) with presence of urine albumin (52.86%) ($p<0.001$). Majority of the women in group C (67.14%) had pre-eclampsia and complications compared to 32.86% in group A and 18.57% of in group B ($p<0.001$). The median gestational age at delivery was statistically similar in all the three groups ($p=0.981$). Most of the women (37.14%) of the women in group C delivered before 38 weeks of gestational compared to 18.57% in group B and 21.43% of in group A ($p=0.032$). In group C, 21.43% of the babies required NICU admission compared to 11.43% in group A and 8.57% of in group B ($p=0.065$). The common indication being preterm birth and low birth weight. Statistically significant difference was observed with respect to NICU stay ($p=0.029$).

Conclusions: High dose calcium, vitamin D3 combined with low dose aspirin, has significant benefit in preventing the pedal oedema and presence of urine albumin, regulating blood pressure at the time of delivery thereby PE with its associated complications and neonatal morbidity in terms of shorter duration of NICU stay.

Keywords: Calcium supplementation, Hypertensive disorders of pregnancy, Maternal outcome, Neonatal outcome, Preeclampsia, Vitamin D

INTRODUCTION

Pregnancy is a physiological phenomenon for most of the women but few develop complications during its evolution which results in adverse maternal and fetal outcomes. Hypertensive disorders of pregnancy (HDP) are one such

disease that causes the most detrimental effects to the maternal, fetal, and neonatal organs.¹ Hypertensive disorders are one of the most common medical condition complicating pregnancy and is a part of a deadly triad, along with hemorrhage and sepsis.² The incidence of hypertensive disorders ranges from 2-8% of all

pregnancies and contributes to 9% of maternal mortality in Asia and 12% in India.^{2,3} Pregnancy induced hypertension is one of the most common causes of both maternal and neonatal morbidity.⁴

Pre-eclampsia (PE)/eclampsia accounts for more than 50,000 maternal deaths worldwide each year.^{5,6} The incidence of PE varies widely from 5-15%.⁷ The incidence in primigravida is about 10% and in multigravida about 5%.⁸ Pregnancy induced hypertension is hypertension that develops as a direct result of gravid state.

The term HDP includes gestational hypertension, PE, and eclampsia.⁸ Increase in systolic blood pressure (BP) by 30 mm Hg or increase in diastolic BP by 15 mm Hg over previously known BP is called HDP. Gestational hypertension is diagnosed when the BP is more than 140/90 mm hg in the absence of proteinuria or pathologic edema. PE is considered severe when proteinuria exceeds 4 gm/24 hours; blood pressure is 160/110 and/or severe headache, visual disturbances or epigastric pain is noted. Eclampsia is the development of generalized seizures in a patient of HDP.⁷

PE is a multisystem disorder of the mother that affects the fetus due to uteroplacental insufficiency.⁹ In consequence these fetuses are at risk of intra-uterine growth retardation and may be delivered prematurely.¹⁰ PE is classified as "severe PE" with any of the conditions viz. blood pressure above 160/110 mm Hg, thrombocytopenia, impaired liver function, renal insufficiency, fetal growth restrictions. PE with or without severe features can progress to eclampsia, hemolysis, elevated liver enzymes, low platelet count syndrome also may lead to acute renal failure and maternal death.¹¹

Maternal complications due to high blood pressure include cerebral hemorrhage, cortical blindness, cortical and tubular necrosis and abruption. All these complications are directly related to raise BP.¹²

PE can be further classified into preterm PE (with delivery before 37 weeks of gestation) or term PE (with delivery at or after 37 weeks of gestation).¹³

During pregnancy, the maternal coagulation system and platelet activation are altered, causing blood hypercoagulability that can induce microthrombus formation, ultimately leading to preeclampsia. Therefore, anticoagulant therapy plays an essential role in the prevention of PE.¹⁴

The intracellular ionized calcium concentration in platelets and sensitivity to angiotensin 2 are increased in women with PE and there is further increase in platelet concentrations of intracellular calcium in response to arginine vasopressin early in pregnancy. Finally, PE is a hypocalciuric state.¹⁵

The World Health Organization (WHO) strongly recommends 1.5–2.0 g elemental calcium daily from 20+0 weeks of gestation for pregnant women with low dietary calcium intake.¹⁶

Evidence also suggests that, in vitamin D deficiency status, calcium absorption diminishes, leading to an increase in circulating parathyroid hormone. Therefore, it is recommended to evaluate both calcidiol and parathyroid hormone levels to accurately assess vitamin D status.¹⁷

Pregnancy induced hypertension occurs in about 8-10% of pregnant women in India.¹⁵ In west it accounts for approximately 2-5% of all pregnancies.¹⁸

Fetus of preeclamptic women have a fivefold increase in mortality compared with infants without the disorder. PE is responsible for approximately 15% of all preterm births.¹⁹

The specialized care of these premature babies place considerable strain on health care resources of developing nations.²⁰

Prevention of preeclampsia may be primary, secondary, or tertiary. Primary prevention involves avoiding pregnancy in women at high risk for PE, modifying lifestyle or improving nutrients intake in order to decrease the incidence of the disease. Therefore, probably the majority of cases of PE are unpreventable. Secondary prevention is based on interruption of known pathophysiological mechanisms of the disease before its establishment. Tertiary prevention relies on using treatment to avoid PE complications. Magnesium sulfate, for example, is the drug of choice for reducing the rate of eclampsia, but at least 71 women would need to be treated to prevent one case of eclampsia.²¹

Many studies about prevention of PE are based on primary interventions, when applied to whole population: bed rest, restriction of activity or regular exercise, nutritional supplements and measures as reduced salt intake, and antioxidants such as vitamins C and E, garlic, and marine oil. Other studies are based on secondary prevention, when applied to high-risk population, drugs such as diuretics, progesterone, nitric oxide, calcium supplementation, and aspirin.^{21,22}

A meta-analysis including all randomized trials (5 studies) evaluated the effectiveness of aspirin compared with placebo or no treatment in women with an abnormal uterine artery Doppler and clinically relevant perinatal and maternal outcomes.²³

Numerous studies have highlighted the potential benefits of vitamin D supplementation during pregnancy, leading to increased concentrations of 25(OH) D in the blood and a reduced risk of pregnancy complications. Specifically, a higher dose of vitamin D, beginning at 1000 IU daily, is recommended, especially for non-Caucasian] races, high-

risk women with a BMI >30 kg/m², those residing in high latitudes, or those delivering between November and March. It is imperative to establish comprehensive guidelines for supplement use during pregnancy to ensure optimal maternal and fetal health.²⁵

Objectives

Primary objective was to compare the efficacy of high dose calcium, vitamin D3 supplementation with high dose calcium, vitamin D3 combined with low dose aspirin, in prevention of PE.

Secondary objectives were to compare maternal outcome in all the three groups, and to compare fetal outcome in all the three groups.

METHODS

The present study was done in the Department of Obstetrics and Gynaecology, Koppal Institute of Medical Sciences, Koppal, Karnataka State, India.

This study was conducted for the period of one year from January 2023 to December 2024.

The study design was a hospital based prospective comparative study.

Females with gestational age of 12 weeks attending antenatal check up at the Department of Obstetrics and gynaecology, Koppal Institute of Medical Sciences, Koppal, Karnataka State, India.

Sample size calculation

A total of 210 women fulfilling the selection criterion were enrolled. The sample size calculation was done using the formula as below.

$$n = Z^2(1 - \alpha/2) \times P \times Qd^2$$

Where, Z-standard normal variate for 95% confidence interval=1.96-prevalence (p)=3.8% based on the study by Amin et al.²⁴

$$Q = 100 - p = 100 - 3.80 = 96.20\%$$

Where d is the absolute precision=5%.

Therefore,

$$n = 3.8416 \times 365.56/25n = 1404.33/25n = 57$$

Considering attrition rate of 10% the sample size was calculated as follows.

$$n = 57 \times 10\% = 6 = 57 + 6 = 63$$

Based on the above calculations, the minimum sample size required to determine primary outcome was 63 in each group. However, in order to have uniformity in calculation the same was considered as 70 in each group summing to 210 in total.

Pregnant females with an obstetric score of primigravida with the gestational age of 12-14 weeks were included in the study. Those with score of multigravida or cases of chronic hypertension, chronic renal disease and women not consenting were excluded from the study. The selected women were divided into three groups of 70 each as: group A: women in this group received high dose calcium 1 g BD and high dose vitamin D3-250 units BD, group B: women in this group received high dose calcium-1 g BD, high dose vitamin D3-250 units BD and low dose aspirin 75 mg OD, and group C: women in this group were given routine antenatal medications.

The pregnant women who fulfilled the selection criterion were explained about the nature of the study in their vernacular language and a written informed consent was obtained prior to the enrollment. Eligible women who fulfilled the selection.

Doppler were interviewed and information regarding age, sex, place, and occupation, and address, obstetric and medical history were obtained. General physical examination including vitals and clinical signs and symptoms were noted. All the women underwent routine investigations including complete blood count, blood group and Rh typing, renal and liver functions tests, bleeding and clotting time, serum LDH, urine analysis and any other investigations wherever indicated. The selected women were followed till delivery and they were monitored for complications of preeclampsia.

Statistical tool

The data obtained was coded and entered into Microsoft Excel Worksheet. The data was analysed using statistical software statistical package for the social sciences (SPSS) version 20.0. Continuous variables were analyzed for normality by the Kolmogorov Smirnov test. The data was expressed in terms of mean±standard deviation (SD) for the data that followed normal distribution and the data which followed skewed distribution was expressed as median and interquartile range (IQR). The comparison of various parameters was done using either Chi-square test or Fisher's exact test. The comparison of continuous data was done using Kruskal Wallis test. At 95% confidence interval (CI), a probability value ('p' value) of less than or equal to 0.050 was considered as statistically significant.

RESULTS

Demographic data

In the present study 55.71%, 50.00% and 52.86% of the women in group A, B and C were aged between 21 to 25

years respectively. However, the age distribution of the women in all the three groups was statistically similar ($p=0.913$).

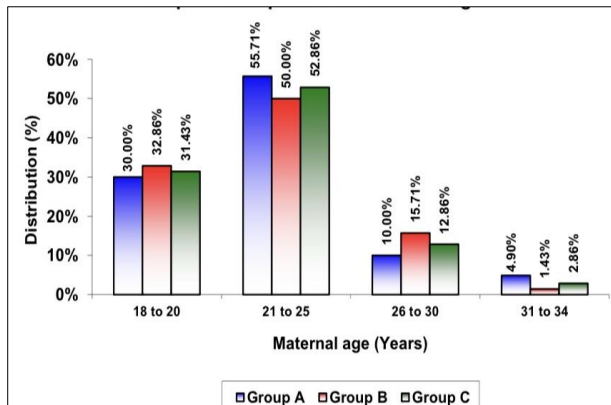


Figure 1: Comparison of maternal age.

The comparison of median systolic and diastolic blood pressure is as shown in Table 1. Statistically significant difference was noted with respect to both median systolic and diastolic blood pressure ($p<0.001$).

In this study 67.14% of the women in group C had pre-eclampsia compared to 32.86% in group A and 18.57% of in group B. This difference was statistically significant ($p<0.001$) (Table 2).

In the present study maternal complications were noted in 67.14% of the women in group C compared to 32.86% in group A and 18.57% of in group B. This difference was statistically significant ($p<0.001$) (Table 3).

In the present study 37.14% of the women in group C delivered before 38 weeks of gestational compared to 18.57% in group B and 21.43% of in group A. This difference was statistically not significant ($p=0.032$) (Table 4).

Table 1: Comparison of blood pressure.

Blood pressure	Groups						P value
	Group A (n=70)		Group B (n=70)		Group C (n=70)		
	Median	IQR	Median	IQR	Median	IQR	
SBP	120	20	120	20	130	20	<0.001
DBP	80	12.5	80	20	90	20	0.001

Table 2: Comparison of antenatal preeclampsia.

Antenatal preeclampsia	Groups					
	Group A		Group B		Group C	
	No	%	No	%	No	%
Present	23	32.86	13	18.57	47	67.14
Absent	47	67.14	57	81.43	23	32.86
Total	70	100	70	100	70	100

Table 3: Comparison of antenatal complications.

Complication	Groups					
	Group A		Group B		Group C	
	No	%	No	%	No	%
Present	23	32.86	13	18.57	47	67.14
Absent	47	67.14	57	81.43	23	32.86
Total	70	100	70	100	70	100

Table 4: Comparison of gestational age at delivery.

Parameters	Groups						P value
	Group A (n=70)		Group B (n=70)		Group C (n=70)		
	Median	IQR	Median	IQR	Median	IQR	
Gestational age (weeks)	38	1	38	1	38	2	0.981

DISCUSSION

Earlier, Taherian et al showed that prescription of low-dose aspirin or calcium-D during pregnancy in healthy

nulliparous women is effective in reducing the occurrence of preeclampsia.²⁶ In a randomized controlled clinical trial on 272 healthy nulliparous woman reported by Khan et al to assess the effect of supplementation of high dose of

calcium (2 gm) in prevention of PE showed that calcium intake is beneficial for both pregnant women and her unborn child.²⁷

Atallah et al reported a review from France on the pharmacodynamics of aspirin, its main effects according to dosage and gestational age, and the evidence-based indications for primary and secondary prevention of PE. Authors concluded that, low doses of aspirin are effective in secondary prevention of PE in mainly those with a history of PE.²⁸

The WHO forecasts the incidence of preeclampsia to be seven times higher in developing countries (2.8% of live births) than in developed countries (0.4%). PE is classified as early-onset and late-onset PE and these subtypes may represent different forms of the disease. The pathogenesis of PE is not completely clear.²⁹

It is evident that, anticoagulant therapy plays an essential role in the prevention of PE. The results have suggested that calcium supplements (≥ 1 g/day) could lower the risk of preeclampsia. As a result, the World Health Organization (WHO) has recommended to supplement calcium for pregnant women especially to high-risk population with a low calcium diet.³⁰

In this study not only PE but even complications were significantly low in women who received calcium and vitamin D supplementation with aspirin (18.57%) compared to slightly less than one third of the women who received only calcium and vitamin D supplementation (32.86%) and in majority of the women who did not receive any medication (67.14%) ($p < 0.001$). Further, non-severe PE was the common complication noted in women with all the three groups but it was high among the women who did not receive any medication (25.71%) than the other two groups (21.43% in group A and 10% in group B). Further, severe PE a serious complications of PE leading to significant morbidity and mortality was also low in women who received calcium and vitamin D supplementation with aspirin (5.71%) compared those who received only calcium and vitamin D supplementation (7.14%) and who did not receive any medication (14.29%). Similarly, lower rate of other complications was observed in women who received calcium and vitamin D supplementation with aspirin that is, imminent eclampsia (0.00% versus 1.43% versus 5.71%), antepartum eclampsia (0.00% versus 1.43% versus 4.29%), abruptio placentae (0.00% versus 0.00% versus 5.71%), HELLP (0.00% versus 1.43% versus 5.71%), IUD (0.00% versus 0.00% versus 1.43%). These observations hypothesize that, calcium and vitamin D supplementation with aspirin helps in preventing PE and its associated complications significantly compared to calcium and vitamin D supplementation alone. Until now, there has been no comparative studies directly assessing the efficacy of supplementation on PE comparing calcium plus vitamin D vs. calcium alone which makes this study unique from

other studies. Hence, direct head-to-head comparison of the observations noted in this study was not possible.

Poon et al for the International Federation of Gynecology and Obstetrics (FIGO) initiative on pre-eclampsia, a pragmatic guide for first trimester screening and prevention showed that nulliparous women who had taken aspirin for more than once a fortnight throughout pregnancy had a lower risk of PE than those who had no reported history of aspirin consumption.³¹

In 2021, Choudhuri et al reported a prospective interventional study from Kolkata, India on 200 primigravidas to evaluate the role of high dose (2000 mg/day) calcium compared to normal dose (1000 mg/day) calcium in preventing the incidence and severity of PE.³²

Serum calcium showed significant negative correlation with systolic and diastolic blood pressure.³³

Gao et al reported a prospective cohort study in which the primary outcome was PE characterized by hypertension as well as proteinuria.³⁴

Sinha et al reported a parallel, open-label, randomized control trial from Eastern India to compare the efficacy of 150 mg versus 75 mg aspirin which concluded a significantly greater number of pregnant females who received aspirin 75 mg (33.92%) developed PE in contrast to those who received aspirin 150 mg (8.77%).³⁵

More recently, a systematic review and meta-analysis by Alsubai et al assessed 25-hydroxyl vitamin D's potential as a possible intervention to lower the risk of PE.³⁶

The network meta-analysis indicated the best supplementation for lowering PE was vitamin D, followed by calcium and calcium plus vitamin D. The findings of this study were also similar with the latest Cochrane review by De-Regil et al.³⁷

The findings of the present study were partly in agreement with the observations reported in a meta-analysis by Imdad et al where, calcium supplementation at a higher dose during pregnancy was associated with a significant 45% reduction of the risk of gestational hypertension {relative risk (RR) 0.55; 95% confidence interval (CI) 0.36-0.85} and 59% of the risk of PE {RR 0.41; 95% CI 0.24-0.69} in the developing countries.^{32,38} The results of this study were also consistent with the observations reported by Levine et al where, the incidence of pre-eclampsia was 6.9% in the calcium group and 0.3% in the placebo group {relative risk -0.94; 95% confidence interval (CI) 0.76-1.16} and concluded that supplementation with 2 gm calcium daily did not reduce the incidence of the severity of preeclampsia or delay its onset.³⁹ An Indian study by Parveen et al showed that high dose calcium supplementation 500 mg three times a day in gestational hypertension significantly reduced the occurrence of PE compared to low dose 500 mg a day calcium

supplementation.^{32,40} The results of this study were strongly in agreement with the observations reported by Parveen et al.⁴⁰

Overall, this maiden study on Indian women comparing the efficacy of high dose calcium, vitamin D3 supplementation with high dose calcium, vitamin D3 combined with low dose aspirin, in prevention of PE shows that, high dose calcium, vitamin D3 combined with low dose aspirin, has significant benefit in preventing the pedal oedema and presence of urine albumin, regulating blood pressure at the time of delivery thereby PE with its associated complication and neonatal morbidity in terms of shorter duration of NICU stay. However, these observations require further validation due to potential limitations of this study.

CONCLUSION

Based on the results of this study it may be concluded that, high dose calcium, vitamin D3 combined with low dose aspirin is highly efficacious in preventing PE. It has also significant benefit in improving maternal outcome in the form of preventing the pedal oedema, presence of urine albumin, regulating blood pressure at the time of delivery thereby PE with its associated complications and neonatal outcome in terms of shorter duration of NICU stay.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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