Original Article

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# Role of High Dose Calcium Supplementation in Pre-eclampsia: A Pilot Study

Obstetrics and Gynaecology Section

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## ABSTRACT

**Introduction:** Pre-eclampsia is a serious condition complicating pregnancy. It is a multisystem disorder responsible for significant maternal and perinatal morbidity and mortality. Thus, prevention of pre-eclampsia may improve both maternal and foetal outcomes. It has been found that reduced serum calcium level may cause high blood pressure by stimulating parathyroid hormone, rennin release and also by producing vasoconstriction in smooth muscle.

**Aim:** 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 pre-eclampsia.

**Materials and Methods:** This was a pilot study and this prospective interventional study conducted from January 2017 to June 2018 in Kolkata, India with 200 primigravidas. About 100 women were given 1000 mg calcium and 100 women were given 2000 mg (high dose) calcium in a day. Incidence of gestational hypertension, pre-eclampsia, severe pre-eclampsia, neonatal outcome etc were assessed in both the groups. Normally distributed data were compared with Student's unpaired t-test. p-value was considered statistically significant when ≤0.05.

**Results:** There was a significant reduction in the incidence of pre-eclampsia (p-value=0.03) among the cases receiving high dose calcium, without any statistically significant reduction in severity of it. There was no reduction in incidence of gestational hypertension with high dose calcium. In neonatal outcome, there was better APGAR score in the high dose group compared to control group (16% in cases and 7% in control group, p-value=0.04).

**Conclusion:** This pilot study paves the way for larger studies to study the role of high dose of calcium which may have a significant role in reduction of pre-eclampsia.

**Keywords:** Eclampsia, Hypertension in pregnancy, Morbidity, Prevention

## INTRODUCTION

Pre-eclampsia is a serious complication of pregnancy usually affecting women in the 2nd and 3rd trimester of pregnancy. It is a multisystem disorder and a potential cause of significant morbidity and mortality both in the mother and foetus. Based on published data from 1976 to 2015, it is revealed that incidence of pre-eclampsia in India varies from 0.179 to 5% the average being 1.5%. Maternal mortality from pre-eclampsia in 1982 was 14.12%, and in 2010 it was 2.2-9%, showing that maternal mortality is decreasing. Perinatal mortality is still high. In 1984 it was 45% and in 2010 it was 24.5-48% [1]. There is marked geographic variation in the incidence of pre-eclampsia ranging 18.5% in Haryana and 49.4% in Tripura [2].

Pre-eclampsia is defined as a multisystem disorder of various aetiology characterised by development of hypertension to the extent of 140/90 mmHg measured on two occasions at least four hours apart and proteinuria after 20th week of pregnancy in previously normotensive and nonproteinuric women. Proteinuria required to diagnose pre-eclampsia is present when in a 24-hour urine specimen it is ≥0.3 grams, a spot protein (mg/dL)/creatinine (mg/dL) ratio ≥0.3, or a urine dipstick protein of 1+ (if a quantitative measurement is not available) [3]. The International Society of Study of Hypertension in Pregnancy (ISSHP) revised the earlier definition of pre-eclampsia and included involvement of other organ system even when proteinuria is absent. Presence of any one of the maternal organ dysfunction such as: a) renal insufficiency-creatinine ≥90 umol/L or ≥1.02 mg/dL; b) hepatic involvement- elevated liver transaminases Alanine Transaminase (ALT), Aspartate Transaminase (AST) at least twice of upper limit of normal/right upper quadrant or epigastric pain; c) involvement-alteration of mental status, eclampsia, blindness, stroke, hyper-reflexia associated with clonus, severe headache with hyper-reflexia, persistent visual scotoma, haematological complications- platelet <1.5 lac, haemolysis or Disseminated Intravascular Coagulation (DIC) features, uteroplacental dysfunction, foetal growth restriction etc., will be sufficient to diagnose as pre-eclampsia [3].

It has been found that low serum calcium may cause high blood pressure by stimulating parathyroid hormone, rennin release and also by inducing vasoconstriction in vascular smooth muscle. This might have implications in a developing country like India, where a pregnant female's diet contains on an average 400-500 mg which might be inadequate [4].

A Cochrane Pregnancy and Childbirth Group meta-analysis found that women taking high doses of at least 1 gm/day of calcium throughout pregnancy reduced the average risk of high blood pressure (RR, 0.65), significantly reduced the risk of pre-eclampsia (RR, 0.45), and had less chance of premature birth (RR, 0.76). In addition, there was no evidence of adverse effects from taking the daily supplement [5].

However, Levine RJ et al., undertook the calcium for pre-eclampsia prevention trial at five US medical centres, concluded that supplementation of 2 gm calcium daily did not reduce the incidence of the severity of pre-eclampsia or delay its onset, nor did it reduce the incidence of pregnancy associated hypertension without pre-eclampsia [6].

With this background, aim of the study was to evaluate the role of high dose calcium supplementation (2 gm/day) compared to normal dose calcium supplementation (1 gm/day) in preventing the incidence and severity of pre-eclampsia in patients attending outpatient department of tertiary care hospital in Kolkata, West Bengal, India.

## MATERIALS AND METHODS

This prospective interventional pilot study was conducted in the Department of Obstetrics and Gynaecology of Command Hospital (EC), Kolkata, West Bengal, India, from January 2017 to June 2018.

Study was approved by the University ethical committee (vide memo no. WBUHS/DEAN/2017-18/1026).

**Inclusion criteria:** A total of 200 patients were included in the study after taking proper informed consent. Inclusion criteria were primigravida with single intrauterine gestation having blood pressure <130/80 mmHg and urine albumin nil or trace.

**Exclusion criteria:** Exclusion criteria were multiple pregnancy, history of cardiovascular, renal, hepatic, endocrinal, coagulation disorder or any other medical disorder and intolerance to high dose of calcium.

The subjects were then allocated randomly into group A and group B by a random table generated by computer. Group A (cases) was given 2 gm/day calcium supplementation and group B was (control) given 1 gm/day supplementation of calcium. Data was collected in predesigned case record format at the starting and subsequently during follow-up at each antenatal visit which was as per the standard schedule of antenatal visit. Patients were recruited at 14 to 20 weeks of their gestation and were followed-up till delivery. Variable parameters like maternal age, number of antenatal visits, period of gestation when calcium started and weight gain during pregnancy were recorded in predesigned case record format, assessed and compared in both the groups. Various delivery related parameters like gestational age delivery, term or preterm and mode of delivery like vaginal, caesarean or instrumental were recorded, and compared in both the groups. Maternal outcome related parameters like incidences of gestational hypertension, pre-eclampsia and severe pre-eclampsia and need of medications like labetalol and magnesium sulphate were recorded in both the groups. For comparison of foetal outcome between the two groups, the various parameters like birth weight and low Apgar score at one minute were recorded.

## STATISTICAL ANALYSIS

Collected data were entered into a Microsoft excel spreadsheet. For statistical analysis, Statistical Package for the Social Sciences (SPSS) version 24.0. and Graph Pad Prism version 5 were utilised. For numerical variables unpaired t-test and for categorical variables Chi-square tests were used. Once a t value was determined, a p-value could be found using a table of values from Student's t-distribution. The p-value≤0.05 was considered statistically significant.

## RESULTS

Patient's age, number of antenatal visits and the time when calcium was started in pregnancy were similar in both the groups. No significant differences were noted in weight gain in pregnancy, preterm delivery rate or caesarean rate between the two groups studied [Table/Fig-1].

All the parameters studied were similar in both the groups except occurrence of pre-eclampsia [Table/Fig-2].

| Parameters | Cases (n=100) | Control (n=100) | p-value |
|---|---|---|---|
| Maternal age (years) | 25.1±3.7 | 24.96±4.163 | 0.76 |
| Number of antenatal visits | 11.580±2.119 | 11.28±2.716 | 0.38 |
| Period of gestation of starting calcium (weeks) | 14.94±0.952 | 14.78±0.894 | 0.22 |
| Weight gain in pregnancy (kg) | 11.767±2.372 | 12.057±2.191 | 0.37 |
| Gestation age at delivery (weeks) | 38.5±1.4 | 38.5±1.6 | 0.97 |
| Preterm delivery | 8 (8.0%) | 10 (10%) | 0.62 |
| Vaginal delivery | 67 (67%) | 72 (72%) | 0.44 |
| Caesarean | 30 (30%) | 23 (23%) | 0.26 |
| Instrumental delivery | 3 (3%) | 5 (5%) | 0.47 |

**[Table/Fig-1]:** Demography and delivery related parameter comparison between the two groups.
Unpaired t-test used

Control group had significant more number of newborns with Apgar score of ≤6 at one minute [Table/Fig-3].

| Parameters | | Cases (n=100) | Controls (n=100) | p-value |
|---|---|---|---|---|
| Gestational hypertension | | 4 (4%) | 5 (5%) | 0.72 |
| Pre-eclampsia | | 2 (2%) | 9 (9%) | 0.03 |
| Severe pre-eclampsia | | 1 (1%) | 2 (2%) | 0.56 |
| Gestation at onset | <34 weeks | 3 (3%) | 8 (8%) | 0.12 |
| | ≥34 weeks | 3 (3%) | 6 (6%) | 0.30 |
| Labetalol required | | 2 (2%) | 7 (7%) | 0.08 |
| $MgSO_4$ required | | 1 (1%) | 4 (4%) | 0.17 |

**[Table/Fig-2]:** Comparison of maternal outcomes related parameters.
t-test was used to calculate p-value

| Parameters | Cases (n=100) | Controls (n=100) | p-value |
|---|---|---|---|
| Birth weight (kg) | 2.9±0.42 | 2.9±0.48 | 0.96 |
| IUGR | 5 (5%) | 7 (7%) | 0.56 |
| APGAR ≤6/10 | 7 (7%) | 16 (16%) | 0.04 |

**[Table/Fig-3]:** Foetal outcomes comparison between the two groups.
t-test was used to calculate p-value; IUGR: Intra uterine growth restriction

## DISCUSSION

Pre-eclampsia is a major cause of maternal and perinatal mortality and morbidity. In Asia and Africa, nearly one tenth of all maternal deaths are associated with hypertensive disorders of pregnancy. In India, the incidence of pre-eclampsia is reported to be 8-10%. Prevention of pre-eclampsia can help improve maternal and perinatal outcomes. This pilot study was done over a period of one and half years with the aim of studying any role of 2000 mg calcium/day (high dose Calcium) in preventing the incidence of pre-eclampsia in primigravida. Both the groups were similar with regard to age, period of gestation at which calcium started and number of antenatal visits. The two groups did not show any statistical significant difference in their mean weight gain in pregnancy, gestational age at the time of delivery and number of preterm delivery.

In present study, 4 (4%) patients developed gestational hypertension in group A and 5 (5%) patients developed gestational hypertension in group B and the difference was not statistically significant (p=0.721). The development of pre-eclampsia in group B was 9% and that in group A was only 2% which was statistically significant (p=0.03). One out of two patients in group A developed severe pre-eclampsia, and 2 out of 9 patients in group B developed severe pre-eclampsia. No statistical significance has been found in the development of severe pre-eclampsia with high dose calcium supplementation (p=0.56).

Imdad A et al., conducted a meta-analysis from pooled data from 10 randomised controlled trials done in different countries on the role of calcium supplementation during pregnancy in reducing risk of developing gestational hypertensive disorders. The meta-analysis showed that 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 pre-eclampsia {RR 0.41; 95 % CI 0.24-0.69} in the developing countries [7].

Levine RJ et al., undertook the calcium for Pre-eclampsia Prevention Trial at five US Medical Centre. After a strict set of inclusion and exclusion criteria and compliance testing, 4589 nulliparous women were included in double blind trial of calcium supplementation or placebo. They also tried to determine whether calcium supplementation would be more beneficial to women with low dietary calcium intake. On analysing data, the incidence of pre-eclampsia was 6.9% in the calcium group and and 0.3% in the placebo group {Relative Risk -0.94; 95% confidence interval (CI) 0.76-1.16}. They concluded that supplementation with 2 gm calcium daily did not reduce the incidence of the severity of pre-eclampsia or delay its onset [6].

In an Indian study by Parveen S et al., it has been shown that high dose calcium supplementation 500 mg three times a day in gestational hypertension significantly reduced the occurrence of pre-eclampsia compared to low dose 500 mg a day calcium supplementation [8].

### Limitation(s)

This study was done with 100 cases and 100 controls. A larger sample size is required for recommendation of high dose calcium in prevention of pre-eclampsia. Study involved patients visiting to a tertiary care hospital in Kolkata, so it looked into only a section of the population not the whole population. The study recruited pregnant mothers with normal blood pressure at the beginning. Therefore, the result may not be applicable to mothers with high risk factors for developing pre-eclampsia which will in fact target a specific group with better clinical applicability of high dose calcium supplementation. Study was done on primigravida so results may not be applicable for multigravida.

## CONCLUSION(S)

This pilot study has shown beneficial effect of high dose of calcium in prevention of pre-eclampsia in primigravida only. Therefore, more studies with a proper sample size and including multigravida in that sample would be necessary in future studies for better clinical utility.

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