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Comparison of High and Low Dose Calcium Supplementation in Prevention of Hypertensive Disorders of Pregnancy

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ABSTRACT

Calcium supplementation during pregnancy may prevent high blood pressure and preterm labour. Out of 500 women, 480 completed the study. At hospital enrolment, the average systolic blood pressure (SBP) was similar between the two groups (116.10 mm Hg vs. 115.01 mm Hg; P = 0.215), as was the average diastolic blood pressure (DBP) (72.74 mm Hg vs. 72.12 mm Hg; P = 0.301). No significant increase in blood pressure was observed in the majority of pregnant women in either group until delivery. Only 2.5% of women in the low-dose group (LDG - group I) and 1.88% in the high-dose group (HDG - group II) developed pre-eclampsia by the end of the study, with no significant association between different calcium dosages and the occurrence of pre-eclampsia (P = 0.503). Regarding maternal complications, 0.63% of women in the group I and 0.21% in the group II experienced major complications during pregnancy or postpartum, but this was not statistically significant (P = 0.623). Among the 480 women, 475 had term labor, and only 5 had preterm deliveries (before 36 weeks of gestation). No maternal deaths were reported. Our study concluded that calcium supplementation, whether in low or high dose, provides significant benefit for pregnant women. The findings demonstrate a notable advantage in preventing pregnancy-induced hypertension (PIH), preterm labor, premature births, and related complications. Therefore, calcium supplementation is highly effective in preventing PIH, which in turn helps prevent pre-eclampsia and eclampsia. As both low and high dose Calcium are effective in preventing PE and Eclampsia, it may be recommended that low dose calcium supplementation may be helpful in prevention of HDP and have favourable feto-maternal outcome in a low resource setting like ours.

Keywords: Hypertensive disorders of pregnancy (HDP), Blood Pressure, Pre-eclampsia, Calcium.

INTRODUCTION

Hypertensive disorders of pregnancy (HDP), including chronic hypertension, pre-eclampsia (PE), Eclampsia, Gestational Hypertension, and Chronic Hypertension superimposed with PE-Eclampsia, are foremost causes of maternal mortality. Hypertension in pregnancy is defined as a systolic BP ≥140 mmHg or a diastolic BP ≥90 mmHg, confirmed by a second reading at least 20 minutes apart. Managing hypertension in pregnant women involves determining whether the hypertension has developed during pregnancy (after 20th week of gestation) or was it pre-existing. Proper management involves taking a detailed

history, frequent monitoring of blood pressure, lab profiles including urine analysis for proteinuria and vigilant watch for symptoms like visual disturbances, headache, right upper quadrant abdominal pain, and lower-extremity oedema suggesting pre-eclampsia.

Calcium intake during pregnancy is inversely related to gestational hypertension. Calcium supplementation can lower blood pressure by stimulating nitric oxide synthesis, promoting vascular smooth muscle relaxation, and reducing intracellular calcium levels.

It may also prevent preterm labour which involves a complex interaction of calcium, calcitonin, parathyroid hormone (PTH), and 1,25-dihydroxy vitamin D3. It indirectly influences smooth muscle functions by elevating magnesium levels, thereby promoting smooth muscle relaxation and potentially averting preterm labour and delivery.

WHO guidelines recommend pregnant women with low dietary calcium intake to consume 1.5-2 gram of calcium daily. Randomized controlled trials (RCTs) on calcium effectiveness of Calcium supplementation in preventing gestational hypertension and PE have shown mixed results. Some studies found high-dose calcium beneficial for women with low dietary intake of calcium, while others found no significant impact. There is no consensus on the optimal calcium dosage for preventing hypertensive disorders of pregnancy (HDP), prompting ongoing research to evaluate the effect of Calcium in different settings.

MATERIALS & METHODS

A prospective interventional study was conducted in the Department of Obstetrics and Gynaecology at Jawaharlal Nehru Medical College, AMU, Aligarh, from August 2022 to July 2024. After approval by institutional Ethical committee, initially, 500 primigravida women (at 12-16 weeks of gestation) aged between 20-35 years were enrolled after getting informed consent. 13 of them were lost to follow-up, and 07 had pregnancy loss, resulting in 480 of them completing the study. They were randomly divided into Two Groups: Group I- Low Dose Group (LDG) that received 500 mg of calcium supplements twice daily and Group II- High Dose Group (HDG) that received the same tablets thrice daily.

Extremes of age, history of gestational hypertension or pre-eclampsia, systolic BP >140 mm Hg and/or diastolic BP > 90 mm Hg at enrolment, multiple gestation, any comorbidities, and refusal of consent were excluded from the study.

The sample size was calculated using https://epitools.ausvet.com.au accounting for a 5% dropout rate, resulting in an initial enrolment of 500 pregnant women, their detailed demographic and dietary histories were recorded along with routine history and general and systemic examination. Vitals and urine protein levels were monitored and routine ANC investigations were done.

Both groups were followed through at least four ANC visits. Women with elevated blood pressure or deranged lab profiles at any visit were further investigated. Those diagnosed with HDP were monitored further and symptoms of pre-eclampsia or impending eclampsia were carefully watched for until delivery.

Statistical analysis included descriptive statistics, chi-square tests, Fisher's exact test, Pearson's correlation, and t-tests.

P-value of < 0.05 was considered statistically significant. The analysis aimed to determine the effect of both dose of calcium supplementation in preventing HDP and its feto-maternal outcome.

RESULT

There were 240 pregnant women in each group, Group I- LDG that received 1 gram Calcium supplementation and Group II- HDG that received 1.5 gram. The average age of pregnant women in group I was 26.55 years, while in group II was 26.37 years. Majority of women belonged to low socioeconomic class and they had diet deficient in calcium.

Comparison of Average Blood Pressure between LDG and HDG:

The systolic and diastolic blood pressure before and after calcium supplementation were assessed. The average SBP and DBP in Grop I before treatment was 116.10 and 72.74mm Hg and 115.01 and 72.12mm Hg in Group II respectively. During hospital stay it was 117.45 and 74.4mm Hg in Group I and 116.66 and 72.45mm Hg in Group II respectively.

Table 1: Blood pressure record before and after supplementation at each ANC visit:

Blood pressure		Low dose group (n = 240) (I)	High dose group (n = 240) (II)	P value
At enrolment	SBP	116.10 ± 6.2	115.01 ± 5.8	0.215
	DBP	72.74 ± 7.5	72.12 ± 6.8	0.301
At first follow-up	SBP	115.77 ± 6.3	115.03 ± 5.8	0.484
	DBP	72.45 ± 7.3	73.11 ± 6.5	0.280
At second follow-up	SBP	115.44 ± 6.4	115.19 ± 6.6	0.834
	DBP	73.22 ± 7.1	71.97 ± 7.1	0.118
At third follow-up	SBP	115.17 ± 7.2	116.19 ± 6.1	0.020
	DBP	73.25 ± 7.0	74.03 ± 6.8	0.023
During hospital stay	SBP	117.45 ± 10.6	116.66 ± 9.5	0.388
	DBP	74.4 ± 8.8	72.45 ± 8.0	0.011
Postpartum	SBP	116.34 ± 8.5	116.29 ± 8.3	0.947
	DBP	72.47 ± 7.8	72.46 ± 7.8	0.990

A significant association was not found between average Systolic and Diastolic blood pressure and both study groups with p-value >0.05.

Assessment of Proteinuria in both group

The quantification of proteinuria helps in diagnosing, monitoring the progression of the disease, and evaluating the effectiveness of treatment. In our study, Urine protein analysis was done at enrolment and at each follow-up ANC visit using the dipstick method owing to its ease of use and quick estimation.

Table 2: Measurement of urine albumin before and after supplementation at each visit:

Urine albumin		Low dose group (n = 240) (I)	High dose group (n = 240) (II)	p-value
At enrolment	nil	221 (46.04%)	226 (47.1%)	0.471
	traces	19 (3.95%)	14 (2.9%)	
At first follow-up	nil	239 (49.8%)	233 (48.55%)	0.068
	1^+	1 (0.2%)	7 (1.45%)	
At second follow-up	nil	238 (49.6%)	238 (49.6%)	1.00
	traces	2 (0.4%)	2 (0.4%)	
At third follow-up	nil/traces	235 (48.95%)	239 (49.8%)	0.216
	1^+	5 (1.05%)	1 (0.2%)	
During hospital stay	nil/traces	227 (47.3%)	229 (47.7%)	0.835
	$1^+/2^+/3^+$	13 (2.7%)	11 (2.3%)	
Post-partum period	nil/traces	234(48.75%)	233(48.54%)	1.00
	1+	6(1.25%)	7(1.45%)	

The difference was not found to be statistically significant among both study groups with a p-value >0.05.

Maternal Complications observed in both the study group:

49.37% (237/240) of pregnant women in Group I and 49.79% (239/240) in Group II were free of any complications and significant association was observed between maternal complications in the two groups with a p-value > 0.05.

Most had delivered vaginally in both the groups at term gestation and very few were diagnosed with Pre-eclampsia (2 in Group I and 3 in Group II).

Table 3: Maternal outcome observed in both the groups:

Maternal outcomes		**Low dose group (n = 240) (I)**	**High dose group (n = 240) (II)**	**P-value**
Mode of delivery	Vaginal	172 (35.83%)	181 (37.71%)	0.351
	LSCS	68 (14.17%)	59 (12.29%)	
Gestational age at delivery	Term	238 (49.6%)	237 (49.4%)	1.000
	Preterm	2 (0.4%)	3 (0.65%)	
Pre-eclampsia		12 (2.5%)	9 (1.88%)	0.503

Neonatal outcomes observed in both the groups:

Out of a total of 480 new-borns, 19 from group I and 20 from the group II were admitted to the NICU for different indications.

Table 4: NICU admission observed in both the groups:

NICU admission	**LDG (I) (n =240)**	**HDG (II) (n =240)**
NIL	221(46.05%)	219(45.65%)
Meconium aspiration	5 (1.05%)	1 (0.20%)
Low birth weight	4 (0.85%)	7 (1.45%)
Respiratory distress	2 (0.40%)	1 (0.20%)
Neonatal Jaundice	8 (1.65%)	12 (2.50%)

DISCUSSION

Pregnancy significantly increases the need for calcium requirement in our body, as approximately 30 grams of calcium is transferred to the foetus during gestation.[1] The World Health Organization (WHO) strongly recommends Calcium supplementation for pregnant women and this also prevents HDP , marking Calcium to be the first nutritional intervention aimed at preventing HDP which is one of the leading causes of maternal mortality worldwide. Research on the impact of calcium on gestational hypertension and PE has produced conflicting results. In our study, we compared the effect of low-dose (1g) and high-dose (1.5g) calcium in preventing PIH and its associated feto-maternal outcome in a low-resource setting.

Among the 480 pregnant women, the low-dose group (I) (240) had a mean age of 26.55 ± 2.9 years, while the high-dose group (II) (240) had a mean age of 26.37 ± 3.3 years, with both groups being comparable. Dietary intake analysis showed that the majority of them in both groups were taking diet deficient in calcium, with 205 in the low-dose group (I) and 202 in the high-dose group (II).

At the time of enrolment into the study, the average systolic blood pressure (SBP) was comparable between the two groups (116.10 mm Hg vs. 115.01 mm Hg), and so was the average diastolic blood pressure (DBP) (72.74 mm Hg vs. 72.12 mm Hg).

All women in both the groups were monitored through a minimum of 4 follow-up ANC visits, during which besides routine ANC checkups and investigations were done. Urine protein analysis and blood pressure measurements were done vigilantly and recorded at every visit. We did not observe any significant rise in BP in the majority of women in either groups until near term.

There were 2.5% of women in Group I and 1.88% in Group II, with a total of 21 out of 480 pregnant women developing signs and symptoms suggestive of preeclampsia. Most of them didn't present with any complain or symptoms suggestive of hypertensive disorders but were diagnosed incidentally when they presented with other complains

but found to have features suggestive of preeclampsia.

In group I, 5/12 women had raised BP and proteinuria but lab profiles (LFT/RFT/CBC) were normal. 2/12 had only deranged LFT along with raised BP and proteinuria whereas 5 /12 women had both deranged LFT and low platelet count (less than 1 lac) with raised BP and proteinuria. Out of 12 women, 3 were diagnosed with severe pre-eclampsia and received prophylactic Magnesium sulphate however none required HDU/ICU admission or progressed to Eclampsia or any other complications. Their post-partum period was also uneventful.

Among the 9 women in Group II, 7 had only Hypertension and proteinuria without any derangements in lab profiles, 01 pregnant women had deranged LFT along with raised blood pressure and proteinuria and only 01 was diagnosed with severe preeclampsia and received Magnesium sulphate prophylactically but didn't require any HDU/ICU admission or developed any complication.

Among the 480 women, 475 had term labour, and only 5 had preterm deliveries (before 36 weeks of gestation). Most preterm deliveries were due to emergency LSCS indicated due to fetal distress or non-progress of labour. Preterm deliveries were slightly more common in the high-dose group (II) (0.65%) compared to the low-dose group (I) (0.4%).

Only 2.5% of women in Group I and 1.88% in the Group II developed pre-eclampsia by the end of the study, with no significant association between different dosages of Calcium supplementation and the occurrence of HDP. The reduction in progression to pre-eclampsia with calcium supplementation is supported by studies from Shakuntala Chhabra et al.[2] and Parween et al. [3]

Ideally protein estimation is done by 24-hour urine protein estimation, a key indicator of HDP. [4] Women with hypertension typically have less than 300 mg of proteinuria, those with mild pre-eclampsia have between 300 mg and 500 mg, and those with severe pre-eclampsia have over 5000 mg of urine protein in 24 hours. [5] In our study, we measured proteinuria levels using the dipstick method owing to its ease of use and quick estimation.

Maternal complications were infrequent in our study, with 0.63% of women in the low-dose group(I) and 0.21% in the high-dose group (II). Most women delivered vaginally, with a small percentage undergoing emergency C-sections due to other obstetric indications. There were no C-sections due to uncontrolled blood pressure or maternal distress, and preterm deliveries were rare slightly more common in the high-dose group (II).

There was no ICU admission or maternal mortality, aligning with findings from Camargo et al. [6]

Calcium supplementation for pregnant women can significantly reduce the risk of preeclampsia and preterm births, as in studies from Azar Aghamohemmad *et al*., [7] Hacker AN *et al*., [8] Parveen *et al.,* [3] Mouria *et al*., [9] It directly impacts smooth muscles by reducing contractility and preventing preterm labour, as supported by Richard J. Levine *et al*..[10]

In our study, 97% of infants in both groups had a birth weight of 2.5 kg or more. The mean birth weight was slightly higher in the low-dose group (I) compared to the high-dose group (II). A small number of newborns required NICU admission, with some needing immediate care for conditions related to prematurity. Neonatal jaundice was more common in the high-dose group (II), but all cases were managed successfully without severe complications. Our study indicates that calcium supplementation during pregnancy reduces the risk of preeclampsia and preterm births in both the groups. This suggests that calcium supplementation not only plays a role in reducing the incidence of preeclampsia and low birth weight of newborns but also reduces the need for lower segment cesarean sections (LSCS), as supported by the findings of Lucy Mackillop et al.,[11] Parveen et al. [3] Follow-ups in the post-partum period revealed that all mothers and babies were very healthy post-delivery.

We concluded that calcium supplementation during pregnancy improves maternal and neonatal health and not only prevent preeclampsia but also premature birth as supported by Parveen et al. [3]

The factors such as mean age of women, socioeconomic class, dietary deficiency of Calcium, gestational age at enrolment into study was comparable in both the study groups.

There was no significant association among both the study groups in blood pressures, urine protein levels, mode of delivery, gestational age at delivery, birth weight of newborns and incidence of pre-eclampsia (p value>0.05).

This lack of significant association between the two groups (Low Dose Group I and High Dose Group II) suggests that both doses of calcium supplementation (1g/day and 1.5g/day) are equally effective in not only preventing Pregnancy Induced Hypertension and but also major maternal and neonatal complications especially related to preterm labour and births.

CONCLUSION

The study concludes that calcium supplementation, whether in low or high doses, is beneficial for pregnant women. It significantly helps in preventing pregnancy-induced hypertension (PIH), preterm labor, premature births, and related complications.

Therefore, in low-resource settings, even low-dose calcium supplementation may be recommended for the prevention of PIH to achieve same feto-maternal outcome as with high dose.

Declaration by Authors

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