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Effect of Vitamin D2 Calcium Supplementation for Prevention of Preeclampsia and its Severity

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ABSTRACT

Objective: *To evaluate the preventive and therapeutic efficacy of vitamin D_2 calcium supplementationin pregnant women with a predictor of hypertension or diagnosed with gestational hyperten- sion(GH) or preeclampsia(PE) to prevent preeclampsia and its severity.* ***Methods:*** *Pregnant women with a predictor of hypertension (130/80 to 135/85 mm Hg) or diagnosed with gestational hypertension(GH) or preeclampsia (non-severe, some severe) were selected. The study group was provided 3-5 capsules of vitaminD_2 calcium (600-1 500 mg daily in Ca content, 600-1500 IU in Vitamin D_2) 3 times a day at different time points in the 6-34 weeks of gestation, and to observe the clinical improvement including hypertension and proteinuria. The control group was selected from subjects who had received conventional management(home bed rest, antihypertensive, anticonvulsant use, etc.) and was subjected to retrospective analysis.* ***Results:*** *Before the administration of vitaminD_2 calcium, the rate of the low levels of total serum Ca(<76μg/ml) was 53.4%(32 cases), significantly higher($p<0.01$) in the study group than the control one (16.7%, 9 cases), and the rate of high levels of that (>90μg /ml) was significan-tly lower in the study group (23.3%, 14 cases) than the control one(55.5%, 30 cases). When the dose of vitamin D_2 calcium was more than 1 000 mg and the duration of use was more than 4 weeks, all pregnant women delivered more than 37 weeks (28 cases, 46.7%). At the dose of 600-900 mg with a duration of more than 4 weeks, there were 28.3% (17 cases) deliveries in the term and 13.3% (8 cases) preterm deliveries over 34 weeks. Two patients have been stopped(28^{th}, 31^{th} week respectively, severe) with the duration of use less than 3 weeks. Total serum Ca showed significantly higher levels(>90μg/ml, 46.7%) after the admini-stration compared before the use(<76μg/ml: 53.4%, >90μg/ml: 23.3%) in the study group ($p<0.05$). In the study group, the prenatal systolic blood pressure(S) after the administration of vitamin D_2 calcium was 139.50±15.93mmHg, significantly lower(10mmHg, $p<0.05$) compared to the onset period(S: 149.22±17.51mmHg), and diastolic blood pressure (D: 94.36±13.98 mmHg) tended to decrease(5mmHg, $p=0.08$) compared to onset period(D: 99.69±15.50 mmHg). Also BP before delivery in the study group was significantly lower(S: $p<0.01$, D: $p<0.01$, respectively) compared to the control one(S: 156.95±20.27mmHg; D: 106.05±18.17 mmHg). There was no significant difference between onset BP and prenatal BP in the control group. The percentage of undetectable levels of urinary protein after the use of vitamin D_2 calcium (48.3%, 29 cases) was significantly higher($p<0.05$) compared to the pre-use (36.7%, 22 cases), and the detection rate of >1 g/L was 28.4%(17patients), which was significantly lower ($p <0.05$) compared to the pre-use (53.3%, 32 patients). The neonatal birth weight after delivery was not significantly different between the two groups* ***Conclusions****: It is believed that vitamin D_2 calcium (more than 1 000 mg of Ca element, Vitamin D_2 1 000 IU, and longer than 4 weeks of use) can effectively prevent gestational hypertension and preeclampsia and its severity, as well as improving some critical parameters(BP, urinary prot-ein, etc.) and thus is of great value for its use in essential antenatal care to reduce maternal and perinatal mortality.*

Keywords : Vitamin D_2 calcium, Gestational hypertension, Preeclampsia, Total serum Ca.

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1.INTRODUCTION

Hypertensive disorders remain among the most significant and intriguing unsolved problems in obstetrics. These disorders complicate 5 to 10 percent of all pregnancies, and together they are one of the deadly triad-along with hemorrhage and infection-that contributes greatly to maternal mor-bidity and mortality rates. Of hypertensive disorders, the *pre*eclampsia syndrome is the most dangerous.[4,13,14)] New-onset hypertension during pregnancy-termed gestational hypertension is followed by signs and symptoms of preeclampsia almost half the time.

Importantly, more than half of these hypertension-related deaths were deemed preventable.[14,15)] WHO recommendation on calcium supplementation during pregnancy for the prevention of pre-eclampsia and its complications include that in populations with low dietary calcium intake, daily calcium supplementation (1.5–2.0g oral elemental calcium) is recommended for pregnant women to reduce the risk of preeclampsia.[11,12,15)]

Calcium is the most important and abundant element in the maintenance of homeostasis as well as in the body's bone balance.[8)] However, the prevalence of hypertension is high in low calcium in-take individuals.[9)] Studies have reported that high doses of calcium can prevent hypertension from stabilizing cell membranes.[1)] It is included in the antenatal care system based on positive results that high-dose calcium supplementation can prevent hypertension in high-risk pregnant women during prenatal care.[11,12)] In addition, studies on the antihypertensive effects of vitamin D have been widely applied in clinical practice.[2,3,5,10)] We demonstrated that the combination of calcium and vitamin D_2 prevents and treats preeclampsia and its severity.

1. SUBJECTS AND METHODS

1.1. Subjects:

Among pregnant women who were admitted to the outpatient department of the Pyongyang Maternity Hospital from January 2023 to October 2024, 114 pregnant women with a predictor of hypertension (130/80-135/85 mmHg) or a diagnosis of gestational hypertension or preeclampsia were selected.

1.2. Methods:

Pregnant women screened according to the diagnostic criteria[14,15)] for hypertensive disorders of pregnancy were subjected to body weight, blood pressure, urine protein, serum calcium, and periph-eral blood tests.

The study group (60 patients) received orally 3 to 5 capsules of vitamin D_2 calcium every day (600 to 1500 mg Ca per day, Vitamin D_2 600 to 1500 IU per day) at different time points from 6 to 34 weeks of gestation, and was administered immediately after meals and maintained until delivery.

The effect of improving clinical and laboratory findings including hypertension, urinary protein and serum calcium during observation and before delivery was observed.

The control group(54 patients) was selected from subjects who had received conventional manage-ment(antihypertensive, anticonvulsant, home bed rest, etc) and the retrospective analysis was performed.

1.3. Observational Index:

The changes of blood pressure and serum total Ca, urinary protein before delivery and neonatal weight status after delivery were observed.

1.4. Statistical analysis:

Statistical analysis were performed using SPSS 21.0.

2. RESULTS

2.1. Composition of the study population.

The composition of the study groups is shown in Table 1.

Table 1. The composition of the study groups.

Group	Case	DH	GH		PE	
			Non-severe	severe	Non-severe	Severe
Study	60(100.0)	8(13.3)	15(25.0)	4(6.7)	21(35.0)	12(20.0)*
control	54(100.0)	-	7(13.0)	3(5.6)	17(31.5)	27(50.0)

*DH: delta hypertension(BP of normal range), GH: gestational hypertension, PE: preeclampsia, ( ):%, *:p<0.05(compared with control).*

As shown in Table 1, the study group included 13.3% (8 pregnant women) of subjects with a pred-ictor of hypertension and gestational hypertension (GH) did not differ significantly between the study group and control one. Severe preeclampsia (PE) was significantly lower in the study group with 20.0% (12 patients) than in the control one (50.0%, 27 patients) (p<0.05).

2.2. The relationship between the first onset of hypertension and gestational age.

The gestational age at which the first elevation of blood pressure (DH) or hypertension occurred is shown in Table 2.

Table 2. The relationship between the first onset of DH or hypertension and gestational age.

Group	Case	Early onset, week				Late onset, week	
		6~13	14~19	20~27	28~33	34~36	37~
Study	60(100.0)	13(21.7)	8(13.3)	24(40.0) **	13(21.7)	2(3.3)	-
control	54(100.0)	8(14.8)	5(9.3)	5(9.3)	15(27.7)	8(14.8)	13(24.1)

*DH:delta hypertension, Early onset <34 weeks, Late onset ≥34 weeks, ( ):%, **: p<0.01.*

As shown in Table 2, The rate of gestational age at which BP elevation or hypertension occurred firstly was the highest in the study group at 20-27 weeks of gestation (40.0%, 24patients), while the rate after 34 weeks of gestation (38.9%, 21patients) was higher in the control group, with significant differences in gestational age composition between the two groups (p<0.01).

2.3. The level of total serum Ca before the administration of vitaminD$_2$ calcium.

The level of total serum Ca before the administration of vitaminD$_2$ calcium are shown in Table 3.

Table 3. The level of total serum Ca before the administration of vitamin D$_2$ calcium.

Group	Case	Total serum Ca, μg/ml			
		60.0-69.9	70.0-79.9	80.0-89.9	≥90.0
Study	60(100.0)	[63.10±5.94] 15(25.0) **	[73.25±2.63] 17(28.4)	[87.96±1.91] 14(23.3)	[95.20±2.45] 14(23.3) **
control	54(100.0)	-	[73.60±1.82] 9(16.7)	[86.00±3.20] 15(27.8)	[94.05±3.24] 30(55.5)

*[$\overline{X}$ ±SD]: μg /ml, ( ):%, **:p<0.01*

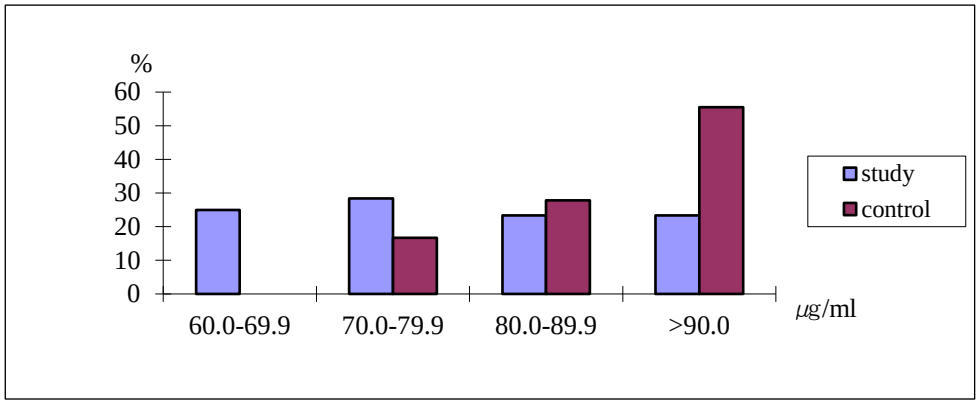

Figure 1. The rate of different levels of total serum Ca before the use of vitaminD_2

As shown in Table 3, the percentage of low levels(<76μg/ml) of total serum Ca was 53.4%(32 patients) in the study group, significantly($p<0.01$) higher than the control one(16.7%, 9patients), and the rate of high levels(>90μg/ml) was 23.3% (14patients) in the study group, significantly lower ($p<0.01$) than the control one (55.5%, 30 patients).

2.4. Relationship between the 1-day dose of vitamin D_2 calcium, the duration of the use and the week of delivery.

The relationship between the 1-day dose of vitamin D_2 calcium and the week of delivery is shown in Table 4.

Table 4. The relationship between the 1-day dose of vitamin D_2 calcium and the week of delivery.

1-day Dose, mg	Case	Delivery week				Artificial abortion※
		~33	34~36	37~38	≥39	
600	15[100.0]	3[20.0]	5[33.3]	7[46.7]	-	1(31w)
900	17[100.0]	1[5.9]	4[23.5]	6[35.3]	6[35.3]	1(28w)
1 000	10[100.0]	-	-	4[40.0]	6[60.0]	
1 200	10[100.0]	-	-	2[20.0]	8[80.0]	
>1 500	8[100.0]			1[12.5]	7[87.5]	

[ ] :%, ※ ( ): week of the artificial abortion.

The weeks of delivery was all over 37 weeks when the dose of vitamin D_2 calcium was over 1 000 mg per day. At 900 mg, the rate of term delivery was 70.6%(12 patients), with a preterm birth rate of 23.5%(4 patients) at 34-36 weeks of gestation and one aborted at 28th week (severe). At 600 mg, the term was 46.7% (7 cases), with a preterm birth rate of 33.3% (5 cases) at 34 to 36 weeks of gestation and a preterm birth rate of 20.0% (3 cases) at less than 33 weeks of gestation, of which 1 (31th week, severe) have been stopped.

Table 5. Relationship between duration, dose of vitamin D_2 calcium and gestational age.

Duration, week	Dose, mg	Case	Delivery week				Artificial abortion※
			~33	34~36	37~38	≥39	
3	600	4(6.70)	3(5.00)		1(1.70)		1[31w]
	900	3(5.00)	1(1.67)	1(1.67)	1(1.67)		1[28w]
4~7	600	6(10.00)		2(3.30)	4(6.70)		
	900	6(10.00)		2(3.33)	2(3.33)	2(3.33)	

Duration,	Dose,	Case	Delivery week				Artificial
	1000~	4(6.70)			4(6.70)		
8~13	600	5(8.30)		3(5.00)	2(3.30)		
	900	6(10.00)			3(5.00)	3(5.00)	
	1000~	16(26.70)			3(5.00)	13(21.70)	
14~	900	2(3.30)		1(1.66)		1(1.66)	
	1000~	8(13.30)				8(13.30)	

( ) :%, [ ]: stopped week of pregnancy

As shown in Table 5, all deliveries were over 37 weeks (28 cases, 46.7%) when the dose of vitamin D_2 calcium was over 1 000mg and the duration of use was over 4 weeks. At 600-900 mg, preterm labor (8 cases, 13.3%) occurred at 34 weeks or more when the length of use was more than 4 weeks, but the term was 28.3% (17cases). Two patients have been stopped (28^{th}, 31^{th} week respectively, severe) with a duration of use less than 3 weeks.

2.5. The change of blood pressure after the use of Vitamin D_2 Calcium

The changes in blood pressure after the use of vitamin D_2 calcium are shown in Table 6.

Table 6. The change of blood pressure after the use of Vitamin D_2 Calcium.

Group	Time	Case	Blood pressure, mmHg	
			Systolic	Diastolic
Study	Onset	60	149.22±17.51	99.69±15.50
	Before delivery	60	139.50±15.93$^{*\#\#}$	94.36±13.98$^{\#\#}$
Control	Onset	54	161.43±21.97	112.86±25.52
	Before delivery	54	156.95±20.27	106.05±18.17

**:p<0.05(compared with onset of hypertenson), $^{\#\#}$:p<0.01(Comparison with prenatal BP in control group).*

As shown in Table 6, in the study group, the prenatal systolic blood pressure(S) after the administ-ration of vitamin D_2 calcium was 139.50±15.93 mmHg, which was significantly lower (10 mmHg, p<0.05) compared to the onset period (S: 149.22±17.51 mmHg). Diastolic blood pressure(D: 94.36±13.98 mmHg) tended to decrease(5 mmHg, p=0.08) compared to onset period(D: 99.69±15.50mmHg). Also BP before delivery in the study group was significantly lower(S: p<0.01, D: p<0.01, respectiv-ely) compared to the control one(S: 156.95±20.27mmHg, D: 106.05±18.17mmHg). There was no si-gnificant difference between onset BP and prenatal BP in the control group.

2.6. Changes in urinary protein after the use of vitamin D_2 calcium.

The changes in urinary protein after the use of vitamin D_2 calcium are shown in Table 7.

Table 7. Changes in urinary protein after the use of vitamin D_2 calcium.

Group	Case	Protein urine, g/L			
		0~0.1	0.3~1.0	1.1~3.0	≥3.1
Before use	60(100.0)	22 (36.7)	[0.80±0.35] 6(10.0)	[1.97±0.70] 23(38.3)	[5.94±2.88] 9(15.0)
After use	60(100.0)	29 * (48.3)	[0.60±0.28] 14(23.3)	[1.92±0.67] 12(20.0) *	[5.92±2.00] 5(8.4)

*[$\bar{X}$ ±SD]:g/L, ( ):%, *:p<0.05(pre-use comparison).*

As shown in Table 7, the percentage of undetectable levels of urinary protein after the use of vitamin D_2 calcium (48.3%, 29 cases) was significantly higher($p<0.05$) compared to the pre-use (36.7%, 22 cases), and the rate of urinary protein reduced below 1.0 g/L(71.6%, 43 cases) was signi-ficantly higher ($p<0.05$) compared to the pre-use (46.7%, 28 cases). The detection rate of >1 g/L was 28.4% (17 patients), which was significantly lower ($p<0.05$) compared to the pre-use (53.3%, 32 patients).

2.7. Changes in the levels of total serum Ca after the administration of vitamin D_2 calcium.

The changes in the levels of total serum Ca after the administration of vitamin D_2 calcium are shown in Table 8.

Table 8. The changes in the levels of total serum Ca after the use of vitamin D_2 calcium .

Group	Case	Total serum Ca, μg /ml				
		60.0-69.9	70.0-79.9	80.0-89.9	90.0-99.9	≥100.0
Before use	60 (100.0)	[63.10±5.94] 15(25.0)	[73.25±2.63] 17(28.4)	[87.96±1.91] 14(23.3)	[95.20±2.45] 14(23.3)	-
After use	60 (100.0)	[67.56±2.38] 6(10.0)	[76.47±3.24] 14(23.3)	[88.35±1.54] 12(20.0)	[97.36±2.41] 18(30.0)	[103.15±2.23] 10(16.7) *

*[$\overline{X}$ ±SD]: μg /ml, ( ):%, *: p<0.05*

As shown in Table 8, total serum Ca showed significantly higher levels (>90μg /ml, 46.7%) after the administration compared before the use (<76 μg/ml: 53.4%, >90 μg /ml: 23.3%) in the study group ($p<0.05$).

2.8. The neonatal birth weight after delivery

The neonatal body weight after delivery is shown in Table 9.

Table 9. The neonatal birth weight after delivery.

Group	Case	Birth weight, g
Study	57	2 747.59±872.50
Control	48	2 836.47±703.22

Study group: Abortion-2, Fetal death-1, Control group: Abortion-2, Fetal death-4.

As shown in Table 9, the neonatal birth weight after delivery was not significantly different between two groups(The study group included high rate of early onsets compared to the control one with high rate of late onsets).

DISCUSSION

In order to maintain a positive calcium balance while providing for mineral transfer to the deve-loping fetus, a pregnant woman needs to assimilate more calcium from the diet than do non-pregnant adults. Thus, the plasma levels of 1,25 dihydroxy vitamin D, possibly of placental origin, are higher during pregnancy to facilitate the absorption of calcium.[9)]

Calcium is known to reduce the risk of preeclampsia but the mechanism of its protective effect remains unknown.[6)] A possible mode of action of calcium could be that it reduces parathyroid hormone release and intracellular calcium, and so decreases smooth muscle contractility and, therefore, vasoconstriction.[7)]

Though Calcium is involved in the mechanisms of increase contractility, it has been shown that at high concentration, calcium ions may cause membrane stabilization in which case the smooth muscle responsiveness decreases. Theoretically, a decrease in membrane permeability to calcium ions caused by increased extracellular calcium concentration stabilizes membranes.

Apparently, administration of high level of calcium ion may become useful either by way of preventing or diminishing pregnancy induced hypertension(preeclampsia).[1)]

Some researchers demonstrated that calcium supplementation prevented endothelial cell activ-ation induced by trophoblastic debris from preeclamptic placentae. The nitric oxide synthase (NOS) pathway and anti-inflammatory effects are involved in the action of calcium on endothelial cell acti-vation.[6)]

Researchers have shown that in human pregnancy the synthesis of NO is increased and that in pre-eclampsia there is a reduction in the plasma concentration and urinary excretion of cyclic GMP.

It is known that NO plays an important role in controlling blood vessel reactivity. This release of NO is dependent on transmembrane ionized calcium flux. The endothelial NO synthase is a calcium-dependent enzyme and demonstrated that small variations in the levels of extracellular ionized calcium, within the physiological range, fundamentally affect NO formation by the vascular endothelium. Any significant decrease in the levels of calcium necessary for this process of adaptation will favour the generation of a hypertensive state. [9)] These findings may suggest, at least in part, the protective mechanism of calcium supplementation on preeclampsia.[6)]

Studies mentioned that pregnant women with low 25(OHD) levels had an increased risk of gestational diabetes, pre-eclampsia, small for gestational age infants and low birth weight infants.

Globally, it is estimated that a significant number of people may be affected either by vitamin D deficiency or insufficiency. Even in areas with abundant sunshine, vitamin D insufficiency or deficiency is extremely common among women.[3)] Vitamin D deficiency increases the risk of dev-eloping hypertension in elderly women, and vitamin D treatment has been shown to reduce systolic blood pressure.[16)]

Our results suggest that calcium and vitamin D combinations may have a beneficial effect to lower the elevated blood pressure by these mechanisms.

CONCLUSION

Vitamin D_2 calcium can prevent preeclampsia or the progression to its severity in pregnant women with a predictor for hypertension or diagnosed with gestational hypertension or preeclampsia. It can also improve some critical parameters (blood pressure, urinary protein, etc.), and it was effective in the dosage of more than 1 000 mg of Ca elements and more than 1 000 IU of VitaminD_2, with the duration of more than 4 weeks.

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Author Contributions

Ryon-Hui Ryong: Literature review, Study design, Screening of Study population and Observation for Study Groups, Analysis of the results and discussion, Research report making **Jong- Rok Paek:** Administration of VitaminD_2-Calcium and Observation for Study Groups **Hye -Yong Choe:** Observation for Study Groups, Analysis of the results and discussion **Kum-Suk Ri:** Laboratory test and statistical analysis

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