

**A RANDOMIZED, VOLUNTEER, PHARMACOKINETIC STUDY COMPARING ABSORPTION AND BIOAVAILABILITY OF CORAL CALCIUM WITH CALCIUM CARBONATE AND CALCIUM CITRATE MALATE SUPPLEMENTS**Varsha Narayanan*¹, Shailesh Pallewar², Abhay Mane² and Amit Bhargava³¹DGM Medical Services, Lupin Ltd, C-5, Laxmi Towers, Bandra Kurla Complex, Bandra East, Mumbai 400051.²Manager Medical Services, Lupin Ltd, C-5, Laxmi Towers, Bandra Kurla Complex, Bandra East, Mumbai 400051.³VP Medical Services, Lupin Ltd, C-5, Laxmi Towers, Bandra Kurla Complex, Bandra East, Mumbai 400051.***Corresponding Author: Dr. Varsha Narayanan**

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ABSTRACT

Introduction: Calcium is one of the vital minerals required by the body and may often be deficient due to multiple factors, requiring intake of calcium supplements. Available calcium supplements vary in calcium salts used and amount of elemental calcium available, dosage strength, as well as the absorption and bioavailability of the calcium present. Calcium from natural coral sources may offer benefits of a possible better absorption due to a bioactive structure. **Objective:** To compare calcium supplements from natural coral sources (coral calcium) with available calcium carbonate (from non-coral sources) and calcium citrate supplements in healthy volunteers by measuring rise in blood calcium and bioavailability, post intake of each of the calcium supplements. **Methodology:** The study was an open label, single centric study comparing 5 groups of 9 volunteers each taking different calcium supplements: two arms of coral calcium supplement tablets of elemental calcium strengths 225 mg and 500mg (Group A, B), 2 arms of non-coral calcium carbonate supplement tablets of elemental calcium strengths 400mg and 500mg (Group C, D), and one arm of calcium citrate malate supplement tablets with elemental calcium 250mg (Group E). Baseline fasting blood and urine samples were taken followed by dosing of the calcium tablet preparation. Blood and urine samples were thereafter collected at 2, 4, 6, and 10 hours to evaluate blood calcium levels, bioavailability and urinary calcium excretion. **Results:** For all groups, peak blood calcium levels were seen at 4 hours. The rise in blood calcium was found to be higher for coral calcium tablets ($P < 0.05$ against tablets of non-coral calcium carbonate and calcium citrate malate). The calculated bioavailability by area under the curve (AUC) was also significantly more for Coral calcium tablets ($P < 0.005$ versus tablets of non-coral calcium carbonate and calcium citrate malate). The urine calcium excretion also increased proportionately over 10 hours for each of the groups. No adverse events were seen in any of the groups. **Conclusion:** Calcium from Coral source may show better absorption and bioavailability as compared to other Calcium supplements containing non coral calcium carbonate and calcium citrate malate.

KEYWORDS: Coral calcium, blood calcium, bioavailability, absorption, calcium carbonate.**INTRODUCTION**

Calcium is the most abundant stored nutrient in the human body.^[1] More than 99% (1.2-1.4 kg) is stored in the bones and teeth while less than 1% is found in extracellular blood calcium. When adults consume calcium as food or supplements, the average absorption rate is approximately 10-30%. The rate can vary widely due to multiple factors. Calcium is distributed among various tissue compartments in the human body. The total blood pool of calcium, approximately 1,200-1,400 mg, is very small but significant as this extracellular pool maintains the plasma calcium level in tight and constant control (typically 8.4-9.5 mg/dL) using a complex interplay of hormones and other substances.

Calcium is required and used throughout the body in small amounts. Research has confirmed that calcium is involved in bone health, vascular and muscle functions, nerve transmission, intracellular signaling, and hormonal secretion.^[2] Each one of these functions could comprise a separate review but as a group illustrate how essential calcium is in the human body. Adequate calcium intakes (1000-1500 mg/d) in adults have been shown in controlled trials to lower the risk of osteoporotic fractures, kidney stones, obesity, and hypertension. Any change in blood calcium affects one or more of all these functions.

Blood calcium does not fluctuate much with changes in dietary intake.^[3] The smallest drop in blood calcium

below the normal level will within minutes trigger the body to transfer calcium from other sources to maintain blood calcium levels and prevent hypocalcaemia. Thus, random blood calcium may sometimes not be an accurate indicator of calcium stores in the body and response of blood calcium to a calcium intake needs to be measured at multiple time points post intake. Also, urinary calcium if done along-side the blood calcium measurements can give further credence that the blood calcium rise is not erroneous and is indeed due to calcium intake.

Cost effectiveness of Calcium supplements not only depend on the amount of elemental calcium available but also the absorption and bioavailability of the calcium in the formulation, and this can be measured by rise in blood calcium at multiple time points after intake.^[4] There are many calcium supplements in the market which vary in the calcium salt used and amount of elemental calcium available, dosage strength as well as the absorption and bioavailability of the calcium in these supplements. There have been recent evidences of benefits of calcium from natural coral sources due to a possible better absorption, as a result of a bioactive microporous structure.^[5-6]

Our study aims to directly compare calcium supplements from these natural coral sources (coral calcium) with available calcium carbonate (from non-coral sources) and calcium citrate supplements in healthy volunteers by

Group A given Tablet A - Coral calcium: Elemental calcium 225 mg
Group B given Tablet B - Coral calcium: Elemental calcium 500 mg
Group C given Tablet C - Non-coral Calcium carbonate: elemental calcium 400 mg
Group D given Tablet D - Non-coral Calcium carbonate: elemental calcium 500 mg
Group E given Tablet E - Calcium citrate malate: Elemental calcium 250 mg

On the day of the dosing, the volunteers were asked to come fasting, and baseline blood and samples were taken. The volunteers were then given the calcium supplement tablet with half a glass (approximately 250 ml) of water.

Post the dosing the volunteers were kept in the rested state and a calcium free breakfast was served to them. Following this blood were withdrawn by the phlebotomist as well as and urine samples collected at 2, 4, 6 and 10 hours. The same was stored in the refrigerators at 4°C and transferred to laboratory for analysis at the end of the sample collection time. For standardization and to avoid errors, the blood samples were taken in the supine position after the volunteer was asked to be in the resting state for 15 minutes. The average blood calcium for each time point for each group was tabulated and plotted to obtain change and rise in blood calcium at peak concentrations compared to baseline. The average bioavailability was calculated by Area Under the Curve (AUC) for each group. To further confirm that blood calcium rise was not erroneous and was indeed due to calcium intake through the supplements, urinary calcium excretion over 10 hours was also done. Volunteers were also monitored for any adverse events throughout their stay at the facility.

measuring calcium rise in blood at multiple time points post intake of each of the calcium supplements, and their bioavailability.

MATERIALS AND METHODS

Healthy male volunteer between the ages of 18 to 45 years of age who provided written informed consent were considered for the study. They were screened for inclusion in the study according to the criteria of BMI of $\geq 18 \text{ kg/m}^2$ and $\leq 25 \text{ kg/m}^2$ with body weight not less than 50 kg, and Systolic Blood Pressure with upper limit less than 140 mmHg and lower limit of more than or equal to 90 mmHg, and diastolic Blood Pressure with upper limit less than 90 mmHg and lower limit more than or equal to 60 mmHg. This was done to maintain intergroup standardization and uniformity of volunteers. The volunteers were also screened for medical history and physical examination performed within 21 days prior to the dosing, by a qualified physician to certify normal health.

The study was an open label, single centric study. Ethical permission was obtained from Independent Ethics Committee. Healthy volunteers were contacted by the volunteer coordinators in batches and were asked to come to the hospital facility in fasting state for the screening after which informed consent was taken for the study. Each batch comprised of 9 volunteers. The following groups were formed post randomization:

RESULTS

The average blood calcium concentrations at baseline and at the various designated time points are plotted for each group (Figure 1). Peak blood concentrations were seen at 4 hours post dosing in all groups (Figure 2). The rise in blood calcium from baseline to 4 hours was seen to be significantly more in the Groups A and B (groups who received Coral Calcium with elemental calcium 225mg and 500mg respectively) as compared to the other groups (Groups C, D and E who received non-coral calcium carbonate 400 mg and 500 mg, and calcium citrate malate 250 mg respectively). $P=0.025$ and $P=0.04$ for Group A versus Group D, and Group A versus Group E respectively, and $P=0.004$ and $P=0.001$ for Group B versus Group C and Group B versus Group D respectively.)

The AUC calculated (Figure 3) was significantly more for the groups receiving Coral Calcium supplements. ($P<0.05$ for Group A, and Group B versus the other groups – C, D and E). The rise in blood calcium corroborated with the rise in urinary calcium over 10 hours, further confirming the response of increase in blood calcium being due to calcium supplement intake. (figure 4). No adverse events or complains were seen by the patients in any of the groups.

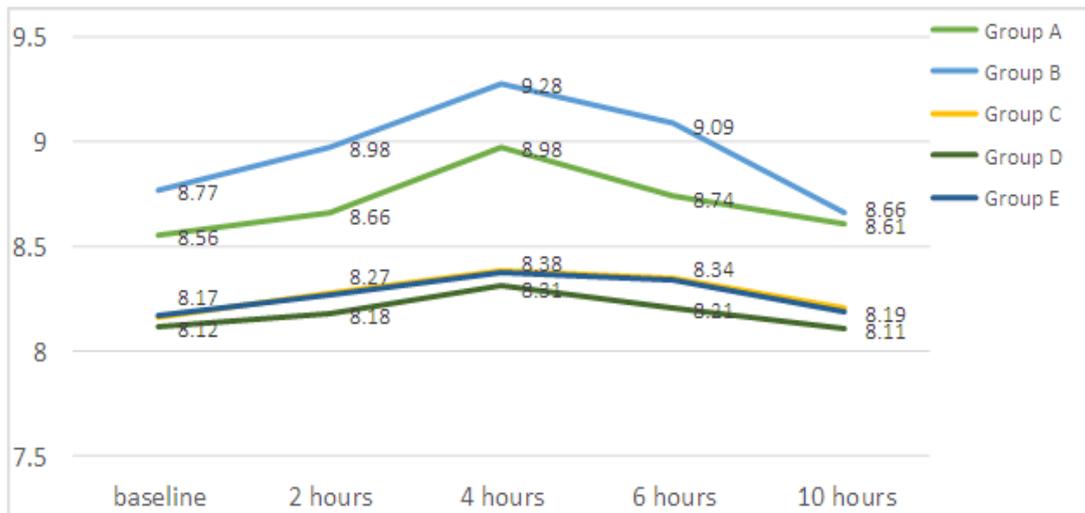


Figure 1: Blood calcium concentrations (mg/dl).

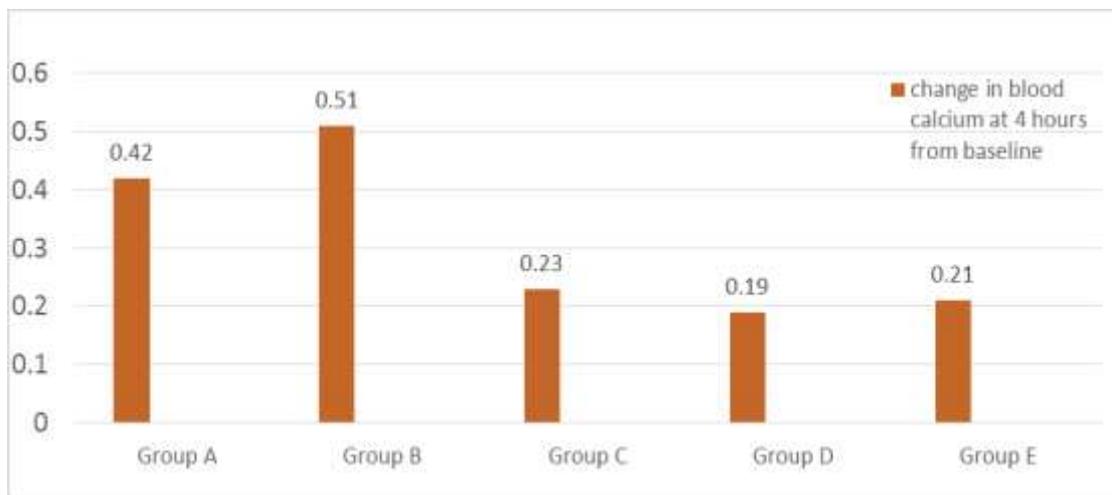


Figure 2: Rise in blood calcium at 4 hours (mg/dl).

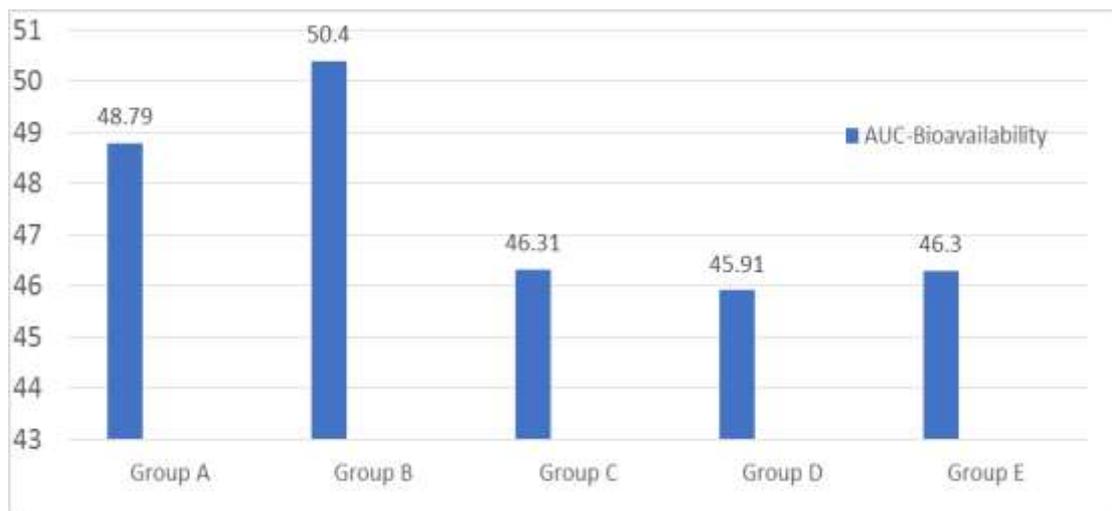


Figure 3: AUC of various calcium supplement tablets.

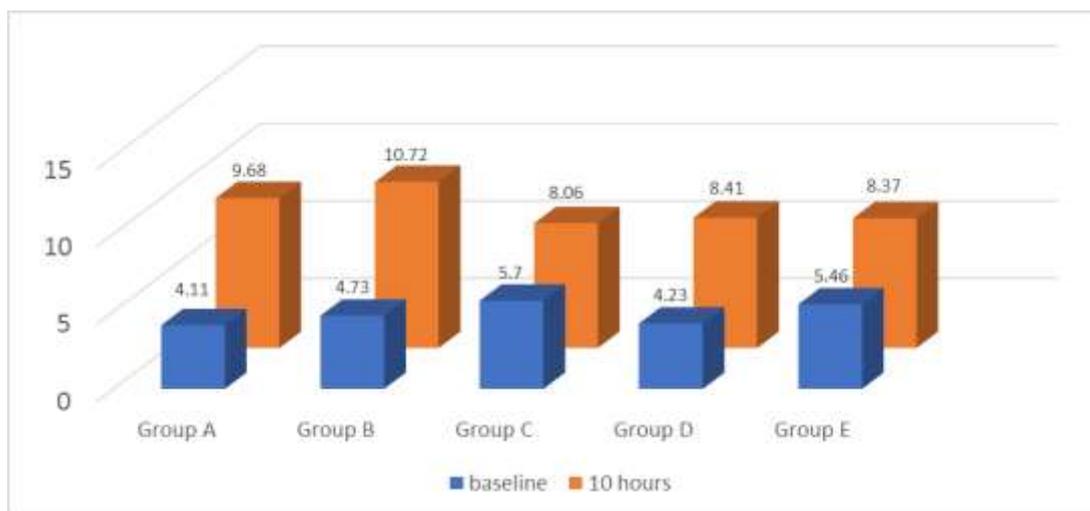


Figure 4: Rise in Urinary calcium from baseline at 10 hours (mg/dl).

DISCUSSION

For many decades there has been advocacy for the use of calcium supplements in prophylaxis and treatment of osteoporosis as well as a supplement during pregnancy. Calcium supplements are commonly taken to achieve intakes of at least 1000-1200 mg/day which has long been recommended for older individuals to treat and prevent osteoporosis. Several preparations of calcium supplements are available commercially, and because of their various rates of disintegration in-vitro and dissolution characteristics, it has been suggested that calcium absorption from different preparations can vary widely. This study demonstrated that the bioavailability of a single dose of coral derived calcium carbonate was greater than that of a single dose of non-coral calcium carbonate and calcium citrate malate in healthy, adult, human volunteers. All the groups showed a nearly similar time to reach maximum concentration in blood, i.e. $T_{max} \sim 4$ hours. Change in total serum calcium and AUC was higher after administration of the coral calcium carbonate versus non-coral calcium carbonate or calcium citrate malate demonstrating superior bioavailability for coral calcium based preparations.

Limited number of clinical studies are available regarding head to head comparison of calcium preparations. In one such study, Wang H *et al* have reported that a single dose of calcium carbonate was more bioavailable than a single dose calcium citrate.^[7] However, we did not find any significant difference in the absorption of calcium from non-coral calcium carbonate (Group C, D) and calcium citrate malate (Group E). In the other study, Ishitani K. *et al* evaluated the mean intestinal absorption of coral-derived calcium in healthy human volunteers with non-coral calcium carbonate by measuring urinary calcium excretion and concluded that, calcium of coral origin is better absorbed from the intestine than calcium of non-coral calcium carbonate origin.^[6]

Findings of the present study are in accordance with these two previous study reports by Wang H *et al* &

Ishitani K. *et al* suggesting greater trend of absorption and bioavailability with coral derived calcium carbonate than non-coral calcium carbonate and calcium citrate malate. Pre-clinical studies also give evidence for better absorption of natural coral calcium compared to Cow bone (hydroxyapatite) calcium and milk calcium.^[8]

The possible reason for better absorption and assimilation of coral calcium carbonate is because of its physicochemical structure, porosity, ionizing ability and particle size. In addition, health benefits are also conferred by the multitude of trace minerals in natural chelated form which work by a biochemic mechanism.^[9] In addition to the findings in these various studies, it has also been reported that rapid swings in blood calcium levels may be less common with the use of coral calcium and other supplements made from marine calcium sources than with conventional calcium supplements.^[10]

Following are some of the limitations of this study. We performed our study in healthy human volunteers and it can be argued that this study could have been done in postmenopausal women or elderly patients. However, based on general recommendations for equivalence studies, we chose to conduct this study in healthy human volunteers as significant variation in absorption is noted in elderly and postmenopausal women. Secondly, this study lacked an un-supplemented control group. Third limitation of our study was having a relatively small sample size. However, this sample size was sufficient to observe a statistically significant difference between the study groups (coral derived calcium group and non-coral calcium carbonate group).

CONCLUSION

Results of this pharmacokinetic study suggested that, calcium from coral source may show better absorption and bioavailability as compared to other Calcium supplements containing calcium carbonate and calcium citrate malate. Encouraging results of the present study thus justifies the need for larger double blind studies.

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