



# Calcitriol supplementation before parathyroidectomy and calcium level after surgery in parathyroid adenoma patients: a randomized controlled trial

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## Abstract

**Background** Hypocalcemia is the most common complication after parathyroidectomy, contributing to extended hospital stays and higher hospitalization costs. The present study aimed to evaluate whether preoperative Calcitriol could help reduce hypocalcemia rates.

**Method** In this randomized controlled trial, we included 80 patients with primary hyperparathyroidism candidates for parathyroidectomy. The intervention group received Calcitriol 0.25 µg/day 1 week before parathyroidectomy. Baseline laboratory data, parathyroid hormone level (before, during, after 5, and 10 min of operation), calcium level (6, 24, and 48 h after operation), and clinical signs and symptoms were recorded.

**Results** Of the 80 participants, 40 (mean age: 53.36 ± 12.97) were randomized to the intervention, and 40 (mean age: 52.84 ± 12.32) to the control group. There were no statistically significant differences in age, tumor size, gender, baseline laboratory data, intra-operative PTH, and calcium level 6 and 24 h after the operation. We observed a significantly higher calcium level in the intervention group 48 h post-operation (8.57 ± 0.30 vs. 8.33 ± 0.38). Also, days of hospital stay and symptomatic hypocalcemia rate were significantly lower in the intervention group.

**Conclusion** In patients with primary hyperparathyroidism, preoperative Calcitriol may be of value in preventing post-parathyroidectomy hypocalcemia and subsequent complications.

**Keywords** Primary hyperparathyroidism · Calcitriol · Calcium · Randomized controlled trial

## Abbreviations

PTH Parathyroid hormone  
PTX Parathyroidectomy

## Introduction

Hypocalcemia is one of the most frequent and, at the same time, critical complications after parathyroidectomy (PTX) [1, 2]. A speculated mechanism for this phenomenon is that after surgery, parathyroid hormone (PTH) levels drop precipitously, resulting in an increase in calcium absorption due to bone remineralization, sometimes called “Hungry bone syndrome” [3, 4]. The prevalence of transient hypocalcemia after PTX due to primary hyperparathyroidism has been reported in 15–52% of patients [3, 5–7]. Also, permanent hypocalcemia has been observed in 0.5–3.8% of cases [5].

Hypocalcemia after PTX has been linked to increased postoperative complications, longer hospital stays, and, subsequently, higher cost of care [8–10]. Therefore, several investigations have been done to elucidate the risk factors for post-PTX hypocalcemia. Higher aged adults, extent of parathyroid removal, evidence of bone disease in radiography, reduction in postoperative parathyroid hormone level, preoperative serum calcium, alkaline phosphatase, and vitamin

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D level have been suggested to play a predictive role in postoperative hypocalcemia [4, 11–13].

Previous studies have indicated that preoperative vitamin D therapy may be beneficial in inhibiting postoperative hypocalcemia and subsequent complications; however, the results were miscellaneous [14–16]. Theoretically, Calcitriol, an active metabolite of vitamin D, enhances calcium uptake in the gut [17]; thus, it is hypothesized that calcitriol supplementation may be of value in preventing postoperative hypocalcemia. In the present study, we conducted a randomized controlled trial to determine whether or not calcitriol supplementation can prevent hypocalcemia after PTX.

## Methods

This randomized controlled trial study was performed in two groups, control and intervention. The study population was all patients with primary hyperparathyroidism who underwent surgery in the surgical ward of Shariati Hospital, Tehran, Iran. For all patients before surgery, demographic and clinical information and levels of PTH, Calcium, Phosphorus, Vitamin D, and alkaline phosphatase were recorded. Patients were randomly divided into two groups for either receiving Calcitriol or not.

In the first group, one pearl of Rocaltrol (calcitriol capsule oral 0.25 µg, Saha Kish Co.) was started daily for patients one week before surgery. The second group did not receive medication. Patients who had hyper parathyroid crisis before surgery and those who had to have all four parathyroid glands removed (patients with MEN) were excluded from the study. Written consent was obtained from both groups of the study. In all patients, sestamibi and preoperative ultrasound were performed, a single-blinded endocrine surgeon operated on all patients, PTH was checked during surgery before incision and 10 min after adenoma resection, and serum calcium was measured and recorded every 6 h after surgery. Calcium supplements were administered in patients with subjective symptoms of hypocalcemia or a level of under mg/dL in oral form and intravenously if calcium levels were under mg/dL.

For sample size estimation, based on a decrease of 18% in calcium levels after the operation ( $11.3 \pm 1.4$  to  $9.2 \pm 0.6$  mg/dL) and an expected further reduction in the intervention group and reach 9.6 mg/dL (about 15% reduction), by considering an 0.05 induction and 80% strength and standard deviation of 0.6 mg / dL, the required sample volume for each group was calculated as 36 participants, and by considering a possible drop rate, the sample size should reach 40 people in each group.

Data processing was performed by SPSS version 21 software (IBM Corp., Armonk, N.Y., USA). Quantitative data distribution was checked for normality. Quantitative

variables were compared between the two groups by independent *T* test or Mann–Whitney *U* test, and qualitative variables were compared by Chi-square. Repeated ANOVA measures were used to compare calcium and PTH levels between intervals. The significance level in the tests was considered at a 0.05 level.

## Results

A total of 80 cases of primary hyperparathyroidism participated in this study, of which 40 were in the control group and 40 in the intervention group. The age of the participants ranged from 34 to 88 years. There was no significant difference between the two groups in terms of gender or age.

As demonstrated in Table 1, there was no significant change between the PTH levels among the two groups; however, the calcium levels were significantly higher among the intervention group after 48 h ( $P=0.002$ ). Also, the hospitalization duration was significantly lower in the intervention group ( $P<0.001$ ).

Among the patients, 39 (48.8%) developed hypocalcemia symptoms. However, this rate was significantly lower among the calcium supplement group ( $P<0.001$ ). There were no cases of life treating hypocalcemia among our patients. Furthermore, there was no significant difference among the average preoperative vitamin D levels of the patients between the normocalcemic and hypocalcemic group ( $P=0.872$ ).

Figure 1 demonstrates the trend of PTH and calcium levels among our patients. Based on statistical analysis, there was a significant change between each interval regarding PTH and calcium levels. The greatest difference was between PTH before incision and 5 min after surgery ( $P<0.001$ ), while the highest calcium change rate was between 6 and 24 h after surgery ( $P<0.001$ ).

Based on repeated measures test, although calcium levels significantly changed throughout the study ( $P=0.020$ ), its changes were not significantly different among the intervention and control group ( $P=0.278$ ). PTH changes was not significant throughout the period of our study ( $P=0.136$ ).

We further analyzed and grouped our patients based on preoperative vitamin D levels of below and above 30 ng/ml. A total of 62 (73.8%) patients had vitamin D levels below 30 ng/ml, with no significant difference between the two groups ( $P=0.813$ ). We analyzed the changes of calcium levels based on the cut-off of 30 ng/ml, and compared the findings among our two groups. Based on repeated measures test, the changes in calcium levels were significant throughout the study period in the below 30 ng/ml group ( $P=0.040$ ), while the changes were not significant in the above 30 ng/ml group ( $P=0.504$ ). However, when comparing the intervention and control group, there was no

**Table 1** Comparison of the demographic and clinical features of parathyroid adenoma patients undergoing parathyroidectomy based on receiving calcitriol supplementation before surgery

Variables	Group; <i>n</i> = 80		<i>P</i> value
	Intervention; <i>n</i> = 40	Control; <i>n</i> = 40	
Age (years); mean ± SD	53.36 ± 12.97	52.84 ± 12.32	0.858
Tumor size (mm); mean ± SD	12.67 ± 4.21	12.05 ± 4.62	0.521
Gender; <i>n</i> (%)			
Male	12 (30.0)	11 (27.5)	0.749
Female	28 (70.0)	29 (72.5)	
On admission laboratory data; mean ± SD			
Calcium (mg/dL)	11.88 ± 1.19	11.81 ± 0.97	0.774
Phosphorus (mg/dL)	2.86 ± 0.84	2.75 ± 0.54	0.479
PTH (pg/mL)	167.14 ± 75.58	163.23 ± 80.11	0.818
Vitamin D (ng/mL)	24.30 ± 13.88	23.55 ± 10.48	0.783
Baseline vitamin D level; <i>n</i> (%)			
< 30 ng/ml	32 (72.7)	30 (75.0)	0.813
≥ 30 ng/ml	12 (27.3)	10 (25.0)	
PTH level changes (pg/mL); mean ± SD			
Before operation	191.95 ± 79.07	190.55 ± 77.89	0.935
Before incision	180.84 ± 81.81.70	190.65 ± 75.47	0.570
5 min after operation	114.36 ± 51.80	116.51 ± 54.48	0.855
10 min after operation	79.81 ± 50.37	72.74 ± 29.12	0.449
Calcium level changes (mg/dL); mean ± SD			
6 h after operation	10.72 ± 0.56	10.86 ± 1.00	0.446
24 h after operation	9.22 ± 0.46	9.20 ± 0.54	0.850
48 h after operation	8.57 ± 0.30	8.33 ± 0.38	<b>0.002</b>
Hypocalcemia symptoms; <i>n</i> (%)	11 (27.5)	28 (70.0)	<b>&lt; 0.001</b>
Hospitalization duration (days); mean ± SD	1.26 ± 0.45	1.77 ± 0.62	<b>&lt; 0.001</b>

*SD* standard deviation, *PTH* parathyroid hormone

Bold values indicate a significant association

significant difference between the two groups regarding the improvement of calcium levels in patients with a vitamin D level of below 30 ng/ml ( $P=0.446$ ). Nevertheless, the calcium levels during the 48 h screening after operation was significantly higher in the intervention group compared to the control group in both the vitamin D below 30 ng/ml and above 30 ng/ml group ( $P=0.016$  and  $P=0.016$ , respectively). Table 2 demonstrates the calcium level changes in our study.

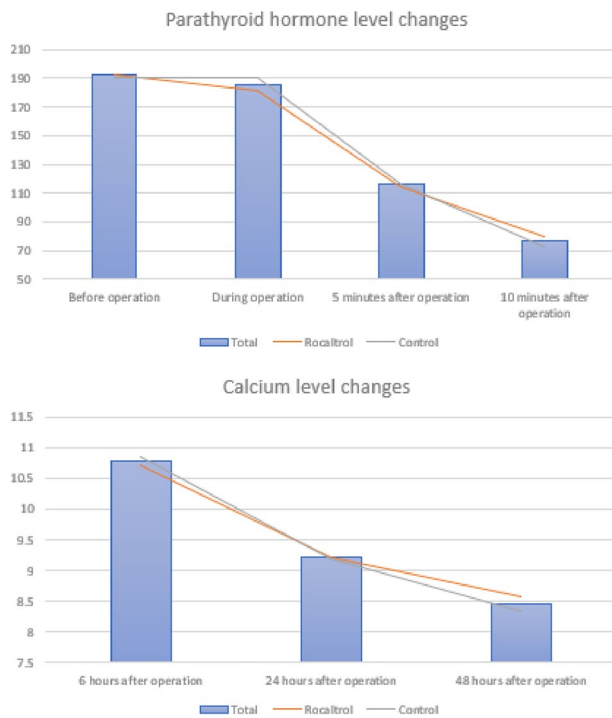
## Discussion

In the present study, we found significantly higher calcium levels 48 h after the operation, lower length of hospital stay, and a lower rate of symptomatic hypocalcemia in the intervention group who received daily Calcitriol 1 week before PTX.

As the most common complication and one of the contributing factors of prolonged hospitalization following PTX [8, 9], hypocalcemia has shown to be sensitive to calcitriol supplementation before or immediately after surgery. A

randomized controlled trial utilizing calcitriol 0.2 µg/day in addition to calcium supplements in secondary hyperparathyroidism patients immediately after surgery has been reported to be effective in decreasing hypocalcemia rate [18]. However, a concern that arises from calcitriol supplementation immediately after surgery is that the beginning of the effects of Calcitriol may be a bit delayed [17]. Hence, preoperative Calcitriol supplementation has been speculated as a possible beneficial strategy. Alsafran et al. showed that preoperative calcitriol therapy of 0.5 µg/day for 5 days before surgery effectively reduces postoperative intravenous calcium therapy and length of hospital stay among patients with renal-origin hyperparathyroidism [16]. Our findings also hinted at the preventive effects of preoperative calcitriol supplementation on postoperative hypocalcemia in primary hyperparathyroid patients.

In terms of hospital stay, we found a longer stay in the control group compared to the calcitriol group. It has been reported that patients who underwent PTX due to secondary hyperparathyroidism and suffered from hypocalcemia post-operation had longer hospital stays (more than eight days on average) [19]. Of note, secondary hyperparathyroidism



**Fig. 1** Parathyroid hormone and calcium changes among hyperparathyroidism patients undergoing surgery based on receiving preoperative Rocaltrol

patients are more prone to postoperative complications than patients with primary hyperparathyroidism [20, 21].

There is still a debate on the appropriate time of discharge after surgery in PTX patients. In a prospective cohort of 3000 PTX patients who were discharged 2.5 h post-operatively, less than 7 percent of the patients showed hypocalcemia, most of whom self-treated with oral calcium [22]. Also, others asserted that the same-day discharge after PTX may be a feasible and safe strategy [23, 24]. As shown in our results, prescribing Calcitriol before surgery may aid in reducing the length of hospital stay.

The intra-operative decreasing trend of PTH has been used as a marker of the successfulness of the surgery [25]. We observed a decreasing trend in parathyroid hormone in the patient during the surgery. This trend was not affected by receiving Calcitriol. Previous studies also indicated no significant effect of vitamin D status on intra-operative PTH levels [26]. However, Mattoo et al. [27] reported the decline of serum intra-operative PTH below a particular cut-off level following surgery has predictive value for hypocalcemia. Lacroix et al. [28] also demonstrated the PTH level 6 h after total thyroidectomy is predictive of hypocalcemia. Clinical evaluation in conjunction with the measurement of serum PTH should be used to assess the likelihood of developing hypocalcemia and the ensuing need for calcium supplementation. Caution to avoid damage to the parathyroid glands should be warranted in these surgeries, which can be assured with techniques such as autofluorescence [29]. The parathyroid gland may be used for further surgeries or even autotransplantation [30]. On the other hand, Randle et al. suggested not to delay the operation because of vitamin D insufficiency, as the patients could be cured as soon as the excision of the parathyroid adenoma [31]. Although it is suggested to correct vitamin D deficiency before surgery to prevent confusion in case PTH is elevated [32].

Also, as total serum calcium can be impacted by a wide range of other parameters like serum albumin levels [33], it may be of significance to utilize ionized calcium levels to have a more accurate understanding of patients post-PTX.

In conducting this study, we adopted a randomized controlled study design to minimize the risk of bias. Also, the baseline data were comparable between the two groups. However, several limitations have to be taken into consideration. Neither the participants nor the researchers were blinded, and the control group did not receive a placebo. Furthermore, we followed the patients until the 48 h post-operation, while there could be episodes of hypocalcemia after the 48 h, which might have gone unnoticed. Another limitation is the lack of urinary calcium evaluation, which could affect vitamin D level modifications.

**Table 2** Calcium level changes among parathyroid adenoma patients undergoing parathyroidectomy based on receiving calcitriol supplementation before surgery based on Vitamin D levels

Variable	Calcium level; mg/dL			
	Baseline	6 h after operation	24 h after operation	48 h after operation
<b>Total</b>				
Intervention	11.88 ± 1.19	10.72 ± 0.56	9.22 ± 0.46	8.57 ± 0.30
Control	11.81 ± 0.97	10.86 ± 1.00	9.20 ± 0.54	8.33 ± 0.38
<b>Vitamin D &lt; 30 ng/ml</b>				
Intervention	11.94 ± 1.26	10.75 ± 0.54	9.28 ± 0.48	8.59 ± 0.33
Control	11.93 ± 0.99	10.81 ± 0.59	9.25 ± 0.56	8.35 ± 0.41
<b>Vitamin D ≥ 30 ng/ml</b>				
Intervention	11.71 ± 1.01	10.63 ± 0.63	9.05 ± 0.37	8.5 ± 0.21
Control	11.48 ± 0.84	11 ± 1.78	9.03 ± 0.48	8.25 ± 0.23

## Conclusion

In this randomized controlled trial, we found that calcitriol supplementation may be beneficial in reducing postoperative hypocalcemia, length of hospital stay, and symptomatic hypocalcemia in primary hyperparathyroid patients. Further studies utilizing various dosages of Calcitriol in longer courses of treatment are recommended to determine the maximum potential of Calcitriol in preventing hypocalcemia and subsequent complications.

**Author contributions** SN, SMMY, and RS designed the study. NM collected the data while RS performed the statistical analysis. RS, AA, and AMA drafted the manuscript. RS, SN and SMMY revised the manuscript. All authors proofread the final version of the manuscript.

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**Availability of data and materials** SPSS data of the participants can be requested from the authors. Please write to the corresponding author if you are interested in such data.

## Declarations

**Conflict of interest** The authors have not disclosed any competing interests.

**Ethical approval and consent to participate** Tehran University of Medical Sciences Human Ethics Committee approved the study (IR.TUMS.MEDICINE.REC.1396.3403). This study was registered in the Iranian registry of clinical trials (Trial number: IRCT20220822055773N2). Written informed consent form was obtained from all the participants enrolled in this trial. All patients' information was de-identified and documented confidentially, and patients were able to exit any time during the trial if they desired. All ethical principles of the Declaration of Helsinki were considered in this trial.

**Consent to publication** Not applicable.

**Informed consent** All participants provided informed consent prior to their participation.

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