Randomized controlled trial of alfacalcidol supplementation for the reduction of hypocalcemia after total thyroidectomy

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KEYWORDS: Total thyroidectomy; Hypocalcemia; Vitamin D; Active vitamin D; Alfacalcidol

The aim of this study was to evaluate the effect of perioperative alfacalcidol on postoperative hypocalcemia after total thyroidectomy.

METHODS: A total of 219 patients scheduled for total thyroidectomy were randomized into groups not receiving (group A) or receiving (group B) perioperative alfacalcidol. Postoperative hypocalcemia was compared between groups on postoperative day (POD) 1 and POD2. Patients with hypocalcemia (<2.00 mmol/L) received oral calcium supplementation. Calcium and vitamin D levels were measured at 5-week and 6-month follow-ups.

RESULTS: The incidence of symptomatic hypocalcemia was significantly lower in group A (P = .02), whereas similarly low levels of calcium were observed in both groups on POD1 (37% and 30%, respectively; P = not significant) and persisted on POD2 (14% and 6%, respectively; P = not significant). Patients with severe hypocalcemia (<1.90 mmol/L) showed faster recovery in group A compared with group B (6% vs 1%, P = .04). At 5 weeks, calcium and vitamin D levels were similar between the groups. Six months after surgery, 4% (group A) versus 0% (group B) of subjects exhibited permanent hypoparathyroidism (P = .04).

CONCLUSIONS: Although the treatment did not correct vitamin D deficiency, perioperative alfacalcidol uptake resulted in decreased transient hypocalcemia and related symptoms in patients undergoing total thyroidectomy.

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The possibility of symptomatic hypocalcemia represents a major issue after total thyroidectomy and can cause significant morbidity. The incidence of hypocalcemia after total thyroidectomy varies widely from 13% to 38%,\(^1\)\(^2\) and the accepted permanent hypocalcemia rate in the literature is 2%.\(^3\) Surgical techniques and surgeons’ levels of experience are important but are not the only factors related to hypocalcemia, and the pathogenesis of early hypocalcemia is multifactorial. The main cause is hypoparathyroidism, resulting from iatrogenic injury to the parathyroid glands caused by ischemia or their inadvertent removal during surgery.\(^3\)\(^4\) Other factors have been associated with an increased risk of hypocalcemia, including age over 50 years, Graves disease, reoperative surgery, lymph node dissection,\(^5\)\(^6\) and vitamin D deficiency.\(^7\)\(^8\) Symptoms occur early in the postoperative course within the first 48 hours, and they prolong the duration of hospitalization as well as the need for biochemical tests. It is not feasible in common practice to select patients who are likely to develop this complication; as a result, some authors have proposed routine calcium and vitamin D administration for each patient undergoing bilateral resection of the thyroid gland, with the aim of decreasing the risk of postoperative hypocalcemia, accelerating hospital discharges, and reducing the costs associated with prolonged hospitalization.\(^9\)\(^10\) However, there is a lack of solid data providing clear evidence for the benefits of such management, and the nature of supplementation therapy is still debated given that multiple forms of vitamin D are available, including calcitriol (1.25-dihydroxyvitamin D3) and alfacalcidol (1α-hydroxyvitamin D3), the 2 most widely prescribed vitamin D analogs. Previous reports have shown that alfacalcidol administration does not affect parathyroid hormone (PTH) secretion after total thyroidectomy.\(^11\)\(^12\) The aim of this randomized clinical trial was to evaluate the efficacy of perioperative routine oral alfacalcidol supplementation in preventing future hypocalcemic crises as well as its effect on the transient and permanent rates of postoperative hypocalcemia after total thyroidectomy.

**Patients and Methods**

A prospective controlled study was performed on consecutive patients undergoing total thyroidectomy or the completion of thyroidectomy from November 2010 to January 2011. Preoperatively, patients were randomly assigned to 1 of 2 perioperative medical treatments: in group A, patients did not receive vitamin D supplementation, and in group B, 2 μg alfacalcidol was administered daily from the day before surgery (D1) to postoperative day (POD) 8 (Fig. 1). None of the patients received calcium supplementation before surgery. After thyroidectomy, the patients were monitored for the following clinical manifestations of hypocalcemia: paresthesia and numbness of the fingertips and perioral area, spontaneous muscle cramps, Chvostek and Trousseau signs in mild forms of neuromuscular irritability, tetany, and/or neuropsychiatric symptoms or cardiovascular symptoms in the case of severe hypocalcemia. Surgeons assessed these symptoms several times a day through clinical examinations, including measurements of serum calcium levels when 1 or more signs of hypocalcemia were present. All patients underwent measurements of serum calcium and vitamin D levels on D1 and calcium examination on POD1. We determined that the measurement of serum PTH levels was not useful in our study because although these levels are predictive of this issue, PTH treatment cannot prevent postoperative hypocalcemia.

We defined postoperative hypocalcemia as a serum calcium concentration lower than 2 mmol/L (normal range, 2.10 to 2.65 mmol/L). All patients with hypocalcemia received oral calcium carbonate (1.54 g in each bag) as follows: 1.54 g 3 times daily for calcium greater than or equal to 1.90 and less than 2.0 mmol/L or 1.54 g 6 times daily for calcium less than 1.90 mmol/L. In patients with calcium less than 2 mmol/L on POD1, serum calcium level measurements were repeated once a day until correction, and calcium supplementation was decreased according to biweekly serum calcium level controls.

For each patient, serum calcium and vitamin D3 levels were routinely measured 5 weeks after surgery. This assessment was repeated 6 months after surgery in cases of postoperative hypocalcemia to evaluate the prevalence of permanent hypoparathyroidism.

All patients underwent total thyroidectomy using identical surgical techniques via a transverse cervicotomy under general anesthesia. Total thyroidectomies were performed by 4 experienced surgeons at the Pitie´-Salpe´trie`re Hospital, Paris, France. The standard procedure was a total thyroidectomy with routine identification of the recurrent laryngeal nerves and parathyroid glands. If 4 parathyroid glands were not observed during the dissection, the resected specimen was examined for the missing parathyroid gland at the end of the procedure. Patients with compromised parathyroid gland vascularization underwent selective parathyroid autotransplantation into the ipsilateral sternocleidomastoid muscle. For patients with recurrent thyroid disease, completion thyroidectomy was performed through the previous cervical scar and followed the same procedure as total thyroidectomy in 1 step. Patients with a preoperative or intraoperative diagnosis of thyroid carcinoma had additional lymph node dissections in both the central and lateral compartments.

During weekly meetings of the scientific committee of the study, patients who were scheduled for a total thyroidectomy for the following week were randomly allocated to one of the treatment groups at a 1:1 ratio. A blinded randomization procedure was performed by an independent researcher using a computerized randomization protocol provided by Microsoft Office Access 2003 software (Microsoft, Redmond, WA); the surgeons were blinded to the alfacalcidol supplementation status. Perioperative and discharge medical prescriptions and follow-ups were performed by anesthetists so that the surgeons were not informed of alfacalcidol intake. These steps were taken to
limit bias in the detection of clinical symptoms of hypocalcemia.

Patients were entered into the clinical trial with a prospective collection of laboratory and clinical data. If a parathyroid adenoma was discovered during surgery for total thyroidectomy, the patient was excluded from the study. If the patient was in group B, alfacalcidol administration was also stopped. Hypoparathyroidism was considered permanent if the patient required oral calcium supplements and vitamin D for more than 6 months with plasma parathyroid hormone levels below 15 ng/L.

Statistical analysis

Results are reported as the median (range) or means ± standard deviation. The primary outcome measure was the presence of postoperative hypocalcemia. Unpaired Student t tests and chi-square tests were used to compare differences between groups. Univariate logistic regression analysis was used to estimate the relationship between hypocalcemia and the following variables: sex, age, total thyroidectomy in 1 or 2 steps, lymph node dissection, final pathology (eg, benign or malignant), and serum calcium and vitamin D levels on D1. A second analysis compared groups A and B to determine factors predictive of the success or failure of alfacalcidol administration with respect to the following outcomes: serum calcium levels on POD1 and 2, the rates of transient and permanent hypocalcemia, and the rates of severe or symptomatic hypocalcemia. Statistical significance was defined as P values less than or equal to .05. All analyses were performed using SAS software (SAS Institute Inc, Cary, NC).

Results

During the study period, 226 consecutive patients were referred for total thyroidectomy and were considered potential candidates for the study. Four patients had concomitant primary hyperparathyroidism and were excluded from the clinical trial, leaving 222 patients in total, with 111 in each group. In group A (no alfacalcidol), 3 patients were excluded from the study because they exhibited parathyroid adenomas discovered during surgery for thyroid disease. There were no associated parathyroid adenomas in group B patients (alfacalcidol). Therefore, 219 patients completed the study (Fig. 1). There were no significant differences in baseline characteristics between the 2 groups (Table 1).
Postoperative hypocalcemia on POD1 was present in 40 patients (37%) in the no-alfacalcidol group (group A) and 33 (30%) in the group receiving alfacalcidol (group B, not significant) (Table 2). On POD2, hypocalcemia persisted in 15 (14%) and 7 (6%) patients, respectively (not significant, $P = .06$). Similar proportions of patients experienced severe hypocalcemia ($<1.90$ mmol/L) in both groups on POD1, but a more rapid recovery of calcemia was observed in the alfacalcidol group given that 6 patients (6%) in group A showed stable calcium levels less than 1.90 mmol/L on POD2 compared with only 1 patient (1%) with stable levels in group B ($P = .04$). Symptomatic hypocalcemia was

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A (no alfacalcidol)</th>
<th>Group B (alfacalcidol)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex ratio (M/F)</td>
<td>19/89</td>
<td>16/85</td>
<td>.52</td>
</tr>
<tr>
<td>Mean age ± SD (y)</td>
<td>52.9 ± 14</td>
<td>53.3 ± 13</td>
<td>.96</td>
</tr>
<tr>
<td>Thyroid disease (n)</td>
<td>66/42 (38.9)</td>
<td>68/43 (38.7)</td>
<td>.97</td>
</tr>
<tr>
<td>Benign/malignant (%)</td>
<td>Papillary 37</td>
<td>43</td>
<td>.07</td>
</tr>
<tr>
<td>Follicular 2</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medullary 3</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graves disease (n)</td>
<td>10</td>
<td>7</td>
<td>.69</td>
</tr>
<tr>
<td>Multinodular toxic goiter (n)</td>
<td>8</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Multinodular euthyroid goiter (n)</td>
<td>48</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>Total thyroidectomy in 1 step (%)</td>
<td>105 (97)</td>
<td>101 (91)</td>
</tr>
<tr>
<td>Lymph node dissection (%)</td>
<td>21 (19)</td>
<td>27 (24)</td>
<td>.38</td>
</tr>
<tr>
<td>Parathyroid autotransplantation (%)</td>
<td>6 (6)</td>
<td>14 (12)</td>
<td>.11</td>
</tr>
<tr>
<td>Preoperative blood tests (D1)</td>
<td>Calcemia ± SD (mmol/L)</td>
<td>2.32 ± .13</td>
<td>2.34 ± .13</td>
</tr>
<tr>
<td>Vitamin D3 ± SD (ng/mL)</td>
<td>20.2 ± 10.9</td>
<td>21.7 ± 14.0</td>
<td>.26</td>
</tr>
</tbody>
</table>

**Table 2** Postoperative outcomes of the 219 patients who had total thyroidectomy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A (no alfacalcidol)</th>
<th>Group B (alfacalcidol)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean calcium serum level ± SD (mmol/L)*</td>
<td>POD1</td>
<td>2.03 ± .14</td>
<td>2.07 ± .13</td>
</tr>
<tr>
<td>POD2</td>
<td>2.04 ± .18</td>
<td>2.12 ± .14</td>
<td>.04</td>
</tr>
<tr>
<td>Postoperative hypocalcemia</td>
<td>POD1 ≤ 2.00 mmol/L, n (%)</td>
<td>40 (37)</td>
<td>33 (30)</td>
</tr>
<tr>
<td>POD2 ≤ 2.00 mmol/L, n (%)</td>
<td>15 (14)</td>
<td>7 (6)</td>
<td>.06</td>
</tr>
<tr>
<td>Severe postoperative hypocalcemia (calcium level &lt; 1.90 mmol/L)</td>
<td>POD1, n (%)</td>
<td>17 (16)</td>
<td>12 (11)</td>
</tr>
<tr>
<td>POD2, n (%)</td>
<td>6 (6)</td>
<td>1 (1)</td>
<td>.04</td>
</tr>
<tr>
<td>Symptomatic hypocalcemia (%)</td>
<td>24 (22)</td>
<td>12 (11)</td>
<td>.02</td>
</tr>
<tr>
<td>Length of hospital stay (d)</td>
<td>2.3 ± 1.4</td>
<td>2.2 ± .9</td>
<td>.65</td>
</tr>
<tr>
<td>Follow-up</td>
<td>Calcium serum level (mmol/L)*</td>
<td>PODD</td>
<td>2.27 ± .13</td>
</tr>
<tr>
<td>Vitamin D (ng/mL)</td>
<td>22.4 ± 12</td>
<td>20.6 ± 14</td>
<td>.14</td>
</tr>
<tr>
<td>6 months after surgery</td>
<td>Permanent hypocalcemia</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

POD = postoperative day; SD = standard deviation.

*Normal ranges for serum calcium levels: 2.10 to 2.65 mmol/L.

†Only for patients with POD1 calcemia less than 2.0 mmol/L and/or for patients with symptoms related to hypocalcemia.

‡Normal ranges for serum vitamin D levels: 30 to 75 ng/mL (severe deficiency under 10 ng/mL).
observed in 24 patients (22%) in group A and in 12 patients (11%) receiving alfacalcidol ($P = .02$). There was a tendency for patients with hypocalcemia-related symptoms to remain in the hospital longer than asymptomatic patients ($2.9 \pm 2.3$ days and $2.1 \pm 7$ days, respectively, $P = .069$). We did not observe any postoperative hypercalcemia, and the maximum serum calcium level on POD1 was 2.40 mmol/L.

Five weeks after total thyroidectomy, serum calcium levels ($2.27 \pm .13$ mmol/L in both groups) and vitamin D levels ($22.4 \pm 12$ ng/mL in group A and $20.6 \pm 14$ ng/mL in group B) were equivalent. There were no significant differences between serum vitamin D levels on D1 and 5 weeks after surgery ($P = .76$).

Six months after surgery, 4 patients (3.7%) required oral calcium supplements and vitamin D with a low level of plasma parathyroid hormone in group A, whereas no patients required these modifications in group B ($P = .04$). Among the 4 patients with permanent hypoparathyroidism, 1 had undergone a total thyroidectomy for a voluminous multinodular toxic goiter (300 g), and the remaining 3 patients had presented with papillary thyroid carcinomas with associated lymph node dissections (TNM classification, 7th edition, 2010: T1bN0, T2N0, and T4aN1b). Three of these patients had parathyroid autotransplantation during surgery because of evidence of parathyroid gland devascularization. The calcium levels on POD1 were significantly lower in the 4 patients with permanent hypocalcemia ($1.80 \pm .14$ mmol/L) compared with the remaining 215 patients ($2.05 \pm .13$ mmol/L, $P = .03$). The difference was even greater for calcium levels on POD2 when comparing the 4 patients with permanent hypocalcemia ($1.71 \pm .08$ mmol/L) with the 36 patients with transient hypocalcemia ($2.10 \pm .15$ mmol/L, $P = .007$). Hypocalcemia was also more severe in symptomatic patients than in nonsymptomatic patients ($1.87 \pm .16$ vs $2.08 \pm .11$) on POD1 ($P < .001$) and POD2 ($2.00 \pm .16$ vs $2.14 \pm .11$), respectively ($P < .001$).

### Comments

In this randomized prospective study, we showed that the perioperative administration of alfacalcidol can effectively decrease the risk of symptomatic hypocalcemia after total thyroidectomy based on a modest but significant increase of calcemia on POD1 and POD2. Moreover, its association with calcium supplementation shortens the recovery time in cases of severe hypocalcemia (<1.90 mmol/L) given that the frequency of this complication was equivalent on POD1 in the 2 groups but was lower on POD2 in the group of patients receiving alfacalcidol. Doses of oral calcium given were higher than those prescribed in previously published studies; however, they corresponded to the practices of our department over the past several years and were based on our prescribing habits before using alfacalcidol. Furthermore, we preferred oral intake to intravenous calcium supplementation, except in cases of severe symptomatic hypocalcemia (eg, Chovstek and/or Trousseau signs). This therapeutic strategy allowed for easier and progressive dose decreases as well as earlier discharge. Dose reduction was achieved progressively based on both clinical and biological follow-ups conducted twice a week to the point of complete weaning. At this point, we have reported any cases of hypercalcemia most likely because high doses are given over a short period given that dose reduction was precocious. Since the completion of this study and with the introduction of alfacalcidol, we have changed our practice by incorporating the systematic perioperative prescription of alfacalcidol. Furthermore, we have reduced the doses of oral calcium to a maximum of 3 packs in cases of severe hypocalcemia.

We also found that postoperative hypocalcemia was higher on POD1 and POD2 in the group that did not receive vitamin D; yet, neither was statistically significant. It could be explained by the fact that postoperative hypocalcemia is a common complication with incidence rates varying from 1.6% to 50%. As a result, it may be worthwhile to include more patients in each group in order to observe statistically significant differences. A lack of power may be responsible for this result, which only shows a trend toward significance. Furthermore, according to Roh et al, the perioperative calcium and alfacalcidol combination may have increased the differences observed in the alfacalcidol group, thereby providing a more effective prevention of postoperative hypocalcemia than alfacalcidol alone given that calcitriol and its derivatives are known to enhance intestinal calcium absorption. However, such a comparison was not the purpose of our study because we first sought to assess the baseline effect of alfacalcidol alone in the prevention of postoperative hypocalcemia after total thyroidectomy.

Both perioperative calcium and vitamin D supplementation have been previously proposed to prevent symptomatic or severe hypocalcemia after total thyroidectomy; however, to our knowledge, our study is the first randomized clinical trial to prospectively evaluate the clinical usefulness of the routine perioperative administration of alfacalcidol alone in a large, homogeneous population of patients referred for total thyroidectomy because of benign or malignant thyroid disease regardless of indication.

The protocol used in this study has the advantage of simplicity because it did not rely on extensive or costly blood tests nor did its planning require a complex algorithm given that the trial started the day before surgery. Although PTH levels can accurately predict postoperative hypocalcemia, serum PTH levels were not measured in our study because these levels have no preventative value. Therefore, we considered PTH measurements to be of limited use in evaluating the efficacy of a perioperative routine of oral alfacalcidol supplementation for the prevention of hypocalcemia. However, serum vitamin D levels were monitored throughout the trial because the regulation of calcemia and PTH secretion by parathyroid glands is an intricate mechanism that does not depend solely on calcium and
phosphate levels. To the contrary, vitamin D is an essential regulator of both PTH secretion and the proliferation of parathyroid cells and is a prominent hormone controlling calcium balance. Any damage to the parathyroid gland, such as that encountered in thyroid surgery, temporarily reduces PTH secretion and predisposes the patient to marked hypocalcemia.

Calcitriol (1,25-dihydroxyvitamin D3) and alfacalcidol (1α-hydroxyvitamin D3) are widely prescribed oral analogs of vitamin D. Although their precise mechanisms are debated, calcitriol therapy seems to significantly suppress PTH synthesis and has a short half-life (12 hours), whereas the half-life of alfacalcidol is 24 hours. These 2 characteristics of alfacalcidol result in high bioavailability and immediate action, which motivated our selection of this vitamin D analog in our study.

Only 1 report has evaluated the efficiency of alfacalcidol in preventing postoperative hypocalcemia after total thyroidectomy. The population was limited to patients with differentiated papillary thyroid carcinoma, and most thyroidectomies were associated with central neck dissection. The authors found that routine postoperative supplementation with 3 g/d oral calcium and 1 μg/d alfacalcidol (beginning on the night of surgery and continuing for 14 days) prevented the increased risk of hypocalcemia associated with central neck lymph dissection. Furthermore, the combination of calcium and vitamin D more effectively prevented postoperative hypocalcemia than calcium alone. These results confirmed, in a select population, the findings of 4 previously published randomized studies that used either calcitriol as a vitamin D analog or vitamin D3 (with no further details) after total thyroidectomy. These studies showed that the oral administration of vitamin D or its metabolites significantly decreases the rates of transient hypocalcemia symptoms. To better clarify the impact of vitamin D supplementation on hypocalcemia after total thyroidectomy, a structured meta-analysis was conducted that included these 4 trials. This meta-analysis evaluated 706 patients and reported a decrease of almost 70% in the rates of symptomatic postoperative hypocalcemia between those treated with vitamin D or its metabolites in combination with calcium compared with patients with no prophylaxis or exclusively receiving calcium. However, these results should be interpreted carefully given their substantial limitations because of the heterogeneity of the studies involved. The clinical characteristics of the studied population varied widely, with subjects presenting with either a highly variable rate of malignancy, ranging from 8% to 83%, or the exclusion of benign disease or previous thyroid surgery. Furthermore, the choice of medication was questionable because the study designs generally used short half-life vitamin D supplements or metabolites.

Given these limitations, we conducted a clinical trial to prospectively evaluate the effect of a long half-life vitamin D supplementation (ie, alfacalcidol) on the rates of postoperative hypocalcemia and its related symptoms by evaluating these factors in each patient referred for total thyroidectomy to control for any major selection bias. We found that alfacalcidol not only decreased the rates of severe and symptomatic hypocalcemia but also allowed for a quicker recovery of serum calcium levels; this effect was expected given that alfacalcidol facilitates calcium absorption during the preoperative period. The length of hospital stay is usually extended in the case of hypocalcemia symptoms, and the administration of alfacalcidol could therefore result in significantly shorter hospital stays. In our study, we also showed that vitamin D deficiency was not corrected by alfacalcidol administration 5 weeks after surgery. This was an expected result because alfacalcidol is not a long-acting or “charging” form of vitamin D. The only form of vitamin D that can correct deficiency is colecalciferol; yet, this form is a long-acting vitamin D with no demonstrated influence on serum calcium levels after total thyroidectomy. Therefore, colecalciferol is of limited use in the reduction of postoperative hypocalcemia.

Our results confirmed that severe hypocalcemia on POD1 and POD2 is associated with hypocalcemia symptoms and is predictive of permanent hypocalcemia. We also found that the risk of permanent hypocalcemia can be decreased with routine vitamin D supplementation; 6 months after surgery, 4 patients from the untreated group developed permanent hypoparathyroidism, whereas none of the patients receiving alfacalcidol developed this complication. This finding is in contrast to a previous study that reported similar rates of permanent hypoparathyroidism in patients receiving routine vitamin D supplementation with calcitriol (either 1 μg or 2 μg daily) in comparison to patients who did not receive calcitriol. Although the 2 groups showed comparable baseline characteristics, the difference found between the groups was significant and must therefore be reported. This is certainly a coincidence and cannot be explained by the effects of alfacalcidol because vitamin D does not improve parathyroid vitality. All of the 4 patients who developed this complication were at high risk for posttraumatic hypoparathyroidism, which is known to be the main factor underlying permanent hypoparathyroidism. Among the 4 patients with permanent hypoparathyroidism, 1 had undergone total thyroidectomy for a voluminous multinodular toxic goiter (300 g), and 3 patients presented with papillary thyroid carcinomas with associated central lymph node dissections. Furthermore, the incidence of permanent hypoparathyroidism after total thyroidectomy is low, ranging from .5% to 2%. Therefore, our results concerning a potential decrease in the rate of persistent hypoparathyroidism with 2 μg daily alfacalcidol should be interpreted very carefully given that the number of patients with this complication was low. Further prospective multicenter studies are warranted to investigate the predictors of permanent postsurgical hypoparathyroidism and to determine the role of routine calcium and vitamin D administration for patients referred for total thyroidectomy.
Conclusion

Our data suggest that perioperative routine administration of alfacalcidol in patients referred for total thyroidectomy tends to decrease the rate of transient hypocalcemia and to accelerate the recovery of hypocalcemia, limiting its severity and reducing the symptoms related to this complication.

References