The American Journal of Surgery (2014) 207, 39-45

The American Journal of Surgery®

Clinical Science

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

Abstract

BACKGROUND: 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 calcemia 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.

The authors declare no conflict of interest.

This paper is based on previous communications from the following meetings: 12th Association Francophone de Chirurgie Endocrinienne Meeting, June 16–18, 2011, Nancy, France; 47th Congress of the European Society for Surgical Research, June 6–9, 2012, Lille, France; and 36th Meeting of the European Thyroid Association, September 8–12, 2012, Pisa, Italy.

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Manuscript received January 18, 2013; revised manuscript May 17, 2013

0002-9610/$ - see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.amjsurg.2013.05.007

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%,[1–3] and the accepted permanent hypocalcemia rate in the literature is 2%.[4] 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.[5,6] Other factors have been associated with an increased risk of hypocalcemia, including age over 50 years, Graves disease, reoperative surgery, lymph node dissection,[7,8] and vitamin D deficiency.[9–11] 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.[12,13] 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.[14,15] 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 calcemia 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 calcemia greater than or equal to 1.90 and less than 2.0 mmol/L or 1.54 g 6 times daily for calcemia less than 1.90 mmol/L. In patients with calcemia 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 Pitié-Salpétrière 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