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ORIGINAL ARTICLE

Terminal ligature of inferior thyroid artery branches during total thyroidectomy for multinodular goiter is associated with higher postoperative calcium and PTH levels

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Summary
Purpose: To evaluate the impact of truncal versus terminal branch ligature of the inferior thyroid artery (ITA) on postoperative calcium and PTH plasma levels in patients undergoing total thyroidectomy for multinodular goiter.
Methods: A prospective randomized study was performed comparing a group of patients that underwent either truncal ligature of the ITA (group 1) or terminal ligature of ITA branches (group 2).
Results: A series of 126 consecutive patients with non-toxic euthyroid multinodular goiter underwent total thyroidectomy. Truncal ligature of the ITA was performed in 63 patients (group 1) and terminal branch ITA ligature in 63 patients (group 2). Postoperative ionized serum calcium (mmol/L) at 24 hours was significantly lower in group 1 than in group 2 patients (1.22 ± 0.06 vs. 1.25 ± 0.05, $P < 0.05$) and at 48 hours (1.20 ± 0.05 vs. 1.23 ± 0.05, $P < 0.05$). Mean postoperative PTH levels (pg/mL) at 4 hours after thyroidectomy were significantly lower in group 1 than in group 2 patients (22.32 ± 11.64 vs. 25.82 ± 12.87, $P = 0.044$). Mean hospital stay (hours) was higher in group 1 than in group 2 patients (87.47 ± 41.04 vs. 70.34 ± 24.82, $P < 0.05$).
Conclusion: This study shows that terminal ligature of ITA branches during total thyroidectomy for multinodular goiter is associated with higher mean postoperative calcium and PTH levels, and shorter hospital stay. However, no significant difference in terms of permanent hypoparathyroidism was observed between the two groups.

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Introduction

Postoperative transient hypocalcemia is observed in 0.4 to 26.8% of patients after subtotal thyroidectomy [1,2]. After total thyroidectomy, an even higher incidence of transient hypocalcemia has been reported in some series ranging from 24 to 45.5% [2—5]. The incidence of permanent postoperative hypoparathyroidism has been estimated at 1.9—2.5% of patients after subtotal thyroidectomy [2,6] and at 0.3—3.5% after total thyroidectomy [2,3,7,8]. Surgeon's experience as well as other criteria have been proposed to explain observed variations in the incidence of postoperative transient permanent hypoparathyroidism. The role of proximal inferior thyroid artery (ITA) ligation or distal ligation of ITA branches has also been proposed but remains controversial. Several previous series reported that truncal ligature of the ITA may not be associated with functional alteration of the parathyroid glands after subtotal thyroidectomy [9—12]. The aim of this study was to prospectively compare the impact of truncal ITA ligature versus terminal ligature of ITA branches on postoperative calcium and parathyroid-hormone (PTH) levels in patients undergoing total thyroidectomy.

Materials and methods

A prospective randomized study of consecutive patients with euthyroid bilateral multinodular goiter was performed in the department of general surgery and organ transplantation at the university of Palermo between January 2006 and January 2009. Preoperative work-up included clinical examination, neck and thyroid ultrasound scan, as well as assay of TSH and thyroid hormone. A preoperative assessment of vocal cord mobility (indirect laryngoscopy) was made in all patients. Indications for total thyroidectomy were tracheal and/or oesophageal compression as well as large sized nodules (> 3 cm). Patients with thyroid cancer (either suspected preoperatively or confirmed by histology), associated parathyroid diseases, age less than 18 years, skeletal diseases, and previous blood transfusions were excluded. We also excluded patients in which the histological examination of the thyroid showed the presence of parathyroid tissue within the thyroid specimen.

Once eligibility was assessed and patient's consent was obtained, participants were randomized, using a secure web-based system that was maintained by the coordinating center, and enrolled in one of the two study arms: ITA trunk ligature (group 1) and terminal branch ITA ligature (group 2). Randomization was stratified by age and sex.

All procedures were performed with the same protocol of general anesthesia. In group 1 patients, ITA truncal ligature was performed lateral to the recurrent laryngeal nerve on both sides. In group 2 patients, terminal branches of the ITA were ligated close to the thyroid capsule and medial to the recurrent laryngeal nerve. The recurrent nerves as well as the inferior and superior parathyroid were carefully exposed and preserved for secure visualization. All procedures were performed by a single surgeon. Operating time was evaluated from skin incision to the last skin suture. In all patients, determination of ionized calcium, serum phosphorus and alkaline phosphatase levels was performed preoperatively, at 24, 48, 72 hours and on the 30th day after surgery. Ionized calcium levels were measured by indirect potentiometry with a ion-selective electrode at correction to pH 7.4 using a Nova 7 analyzer (Nova biomedical, Darmstadt, Germany; coefficent of variation 3.5% per x = 1.19 mmol/L). We also evaluated PTH plasma levels at 4 hours after surgery.

Normal range for blood ionized calcium, serum phosphorus and alkaline phosphatase were considered respectively as 1.16—1.32 mmol/l, 2.7—4.5 mg/dl and 64—270 U/L. PTH levels were defined as normal when the PTH was greater or equal to 10 pg/ml. Transient hypocalcemia was defined when the ionized calcium was less than 1.16 mmol/l and when signs and symptoms of neuromuscular irritability required treatment for less than six months, while permanent hypoparathyroidism was diagnosed when the treatment period exceeded six months. Postoperative calcium therapy was started only when the serum calcium levels were less than 1.16 nmol/l and when symptoms of hypocalcemia were present. The mean duration of hospital stay (hours) was also evaluated for each patient. Patients were clinically assessed postoperatively at 24, 48, 72 hours and on day 30 for the presence of Chvostek's and Trousseau's signs and other symptoms of hypocalcemia, such as peripheral or oral paresthesia, seizure, and laryngospasm. All patients underwent clinical and laboratory (ionized serum calcium assay) follow-up at 5 and 8 months postoperatively for potential permanent hypoparathyroidism.

Statistical analysis — mean patient age, operating time, hospital stay, serum ionised calcium, phosphatemia (preoperatively and postoperatively at 24, 48, 72 hours and 30 days) were evaluated and compared between the two groups using Student's *t*-test. Transient hypocalcemia was analyzed by means of the χ^2 test. Fischer's exact test was used for non-parametric data.

Results

A prospective randomized study of 126 consecutive patients who underwent total thyroidectomy for euthyroid bilateral multinodular goiter was performed. In group 1, 63 patients underwent truncal ITA ligature: 16 men and 47 women, mean age 37.2 ± 9.1). In group 2, 63 patients underwent ligature of the terminal ITA branches proximal to the thyroid capsule: 16 men and 47 women, mean age 38.1 ± 10.1). In both groups, the preoperative mean values of ionised calcium and phosphoremia were similar (Table 1). Mean operating time (minutes) was shorter in group 1 than in group 2 (83.6 ± 15.7 [range 68—138] versus 106.3 ± 24.24 [range 84—205]) ($P < 0.05$). No postoperative recurrent laryngeal nerves injuries was observed.

Mean ionized calcium levels were significantly lower in the ITA truncal ligature group (group 1) than in group 2 patients at 24 hours (1.22 ± 0.06 vs. 1.25 ± 0.05, $P < 0.05$) and 48 hours after thyroidectomy (1.20 ± 0.05 vs. 1.23 ± 0.05, $P < 0.05$). However, no statistical difference in ionized calcium levels remained significant between the two groups at 72 hours and 30 days after surgery (Table 1). In addition, serum phosphate levels was significantly higher in group 1 at 24 hours (3.88 ± 0.59 vs. 3.59 ± 0.61, $P < 0.05$) and 48 hours after thyroidectomy (3.98 ± 0.55 vs. 3.70 ± 0.60, $P < 0.05$). Serum alkaline phosphatase levels were within the normal range and similar in both groups preoperatively, at 24, 48, 72 hours after thyroidectomy and on postoperative day 30.

Postoperative hypocalcemia was observed in 31 patients (24.6%) at 24 hours after thyroidectomy in all patients from both groups. Postoperative hypocalcemia occurred significantly more frequently in group 1 than in group 2 (33.3% vs. 15.8%, $P < 0.05$) (Table 2). Mean postoperative

Table 1 Mean preoperative and postoperative serum ionized calcium levels.

Serum ionized calcium	Preoperative	+24 hours	+48 hours	+72 hours	+30 days
Group 1 ($n=63$)	1.257 ± 0.0460	1.221 ± 0.0674	1.203 ± 0.0538	1.236 ± 0.0458	1.243 ± 0.0457
Group 2 ($n=63$)	1.270 ± 0.0405	1.254 ± 0.0551	1.232 ± 0.0548		
	1.246 ± 0.0529	1.252 ± 0.0506			
P	n.s.	< 0.05	< 0.05	n.s.	n.s.

n.s.: non-significant.

Table 2 Parathyroid morbidity rates in group 1 and 2.

	Biological hypocalcemia at day 1	Symptomatic hypocalcemia at day 1	Permanent hypoparathyroidism at 6 months
Group 1 $n=63$ (%)	21 (33.)	8 (12.)	2 (3.1)
Group 2 $n=63$ (%)	10 (15.8)	1 (1.5)	1 (1.5)
P	< 0.05	< 0.05	n.s.

n.s. = non-significant.

PTH level at 4 hours was 22.3 ± 11.6 in group 1 patients and 25.8 ± 12.9 in group 2 patients ($P = 0.044$). Clinical signs of hypocalcemia were observed in 12.6% of group 1 patients (8/63) and in 1.5% of group 2 patients (1/63) ($P < 0.05$). Clinical signs of hypocalcemia were managed by oral calcium gluconate (1 mg/kg per hour) together with 1000 mg/day of intravenous calcium carbonate for two days. Clinical signs disappeared within 96 hours in all patients. No significant difference in terms of permanent hypoparathyroidism was found between the two groups (3.1% vs. 1.5%) (Table 2). Mean hospital stay (hours) was significantly higher in group 1 patients than in group 2 patients (87.5 ± 41.0 vs. 70.3 ± 24.8, $P < 0.05$).

Discussion

Transient and permanent hypoparathyroidism is observed as a surgical complication after total, subtotal or near-total thyroidectomy; this may occur due to excision of one or more parathyroid glands or, due to impairment of parathyroid blood supply subsequent to surgical manipulation [13—15]. Its incidence depends on the type of thyroidectomy, specific thyroid disease, and operating team experience [2,16—18]. Previous reports evaluating parathyroid function in relation to the technique of ITA ligature have mostly involved patients undergoing subtotal thyroidectomy [9—12]. This study involved a homogenous group of patients with euthyroid, bilateral multinodular goiter. All procedures were performed by the same surgeon who performed a total thyroidectomy using identical surgical technique in all patients [2,6,18—24]. We showed that transient hypocalcaemia was observed in a quarter of these patients (24.6%). Postoperative calcium and PTH levels on day 1 were significantly lower in patients who underwent truncal ITA ligature. Consequently, mean hospital stay (in hours) was significantly higher in this group of patients.

In concordance with this study's results, Maralcan et al. reported a transient hypocalcemia rate of 26.5% after subtotal thyroidectomy [12]. For many years, subtotal and total thyroidectomy for multinodular goiter have been considered to have similar postoperative morbidity rates with regard to parathyroid injury [1,2]. Parathyroid arteries are terminal vessels branching off the thyroid arteries; proximal or distal ligature of the ITA during thyroidectomy have been considered to have an impact on parathyroid vascularization and function postoperatively [25]. However, this issue remains controversial. Curtis reported the presence of anastomoses between parathyroid arteries and thyroid glandular tissue, which were spared after subtotal thyroidectomy [26]. Furthermore, several other studies reported that parathyroid vascularization may also be compensated through anastomotic circuits via peritracheal and/or periesophageal arteries [27—29]. Hence, no significant difference in term of postoperative hypocalcemia have been observed after subtotal thyroidectomy between patients undergoing ITA truncal ligature and those undergoing terminal branch ITA ligature [9,12].

We observed in this study that patients who underwent total thyroidectomy with ITA trunk ligature had lower postoperative mean calcium and PTH levels at 24 and 48 hours postoperatively. This discrepancy may be explained by the fact that total thyroidectomy results in damage to anastomotic connections between the ITA and thyroid tissue whereas these circuits remain intact after subtotal thyroidectomy [9—12]. As previously reported, PTH level at 4 hours after surgery was not predictive for clinical signs of hypocalcemia in this study [30]. Lastly, we believe that mean operating time was significantly longer in patients undergoing ligature of ITA terminal branches since dissection and bleeding control were more time consuming [31,32].

In conclusion, this study shows that terminal ligature of ITA branches during total thyroidectomy for multinodular goiter is associated with higher mean postoperative calcium and PTH levels, and shorter hospital stay. However, no significant difference in terms of permanent hypoparathyroidism was observed between the two groups.

Conflict of interest statement

Nothing declared.

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