How to Cite:
Farooque, M., Narola, V., Prajapati, D., & Patel, T. (2023). Prospective evaluation of perioperative biochemical investigations to predict hypocalcemia after total or near total thyroidectomy. *International Journal of Health Sciences*, *6*(S8), 6589–6595. https://doi.org/10.53730/ijhs.v6nS8.13907

Prospective evaluation of perioperative biochemical investigations to predict hypocalcemia after total or near total thyroidectomy

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***Abstract*---**Hypocalcemia is one of the common complications after total thyroidectomy. In these patients, the serum parathyroid hormone (PTH), calcium level decreases, and the phosphorus level increases. The level of fibroblast growth factor-23 (FGF-23), a phosphaturic hormone, increases in the serum to normalize the serum phosphorus level. In our study, we aimed to investigate the predictive values of PTH, calcium, phosphorus, 1,25-dihydroxy vitamin D (vitamin D), and FGF-23 tests in revealing patients who will develop hypocalcemia after thyroidectomy. Fifty-seven patients undergoing total thyroidectomy (fifty-two with multinodular goiter, three with Graves' disease and two with papillary thyroid cancer) were included in this prospective study. Serum PTH, calcium, phosphorus, and vitamin D levels of the patients were measured preoperatively. Ten minutes after complete removal of the thyroid gland, intraoperative PTH (IOPTH) level was measured and the amount of decline in PTH level (PTH decline) was calculated. Postoperative PTH, calcium, phosphorus, vitamin D, and FGF-23 levels were measured 24 h after the operation. Postoperatively, hypocalcemia developed in 7

International Journal of Health Sciences ISSN 2550-6978 E-ISSN 2550-696X © 2023.
Manuscript submitted: 18 Oct 2022, Manuscript revised: 9 Nov 2022, Accepted for publication: 18 Dec 2022

(12.3%) of the 57 patients. IOPTH, postoperative PTH, calcium, and vitamin D levels were significantly lower and PTH decline was significantly higher in patients with postoperative hypocalcemia. Postoperative FGF-23 levels were similar between the groups (p 0.952). When the IOPTH and postoperative serum calcium values were evaluated together, the highest sensitivity and positive predictive values were obtained (93.5% and 67.5%, respectively), The postoperative FGF-23 test was found to be unsatisfactory to reveal development of hypocalcemia (sensitivity of 14.3%). The success of detecting patients with hypocalcemia was highest when IOPTH and postoperative serum calcium levels were evaluated together. The FGF-23 measurements were found to be not sufficient in identifying hypocalcemic patients after total thyroidectomy.

***Keywords*---**thyroidectomy, hypocalcemia, fibroblastic growth factor-23, diagnosis.

Introduction

The surgical treatment of multinodular goiter and thyroid cancer is total thyroidectomy (TT) [1, 2]. Transient hypocalcemia is observed as a postoperative complication in 1 to 50% of patients after thyroidectomy [1, 3, 4]. Hypocalcemia (clinically) has severe symptoms ranging from paresthesia and tingling to cramping and tetany, and convulsions, observed in 20–30% of the patients [5]. Hypocalcemia may develop early at 24– 48 h and as late as 4 days postoperatively [5]. This may often lead to longer hospital stay and require measurements of the serum calcium level. Patients discharged from the hospital with normal serum calcium levels in the early postoperative period may be re-hospitalized due to clinical hypocalcemia symptoms [5, 6]. Therefore, early diagnosis of patients with hypocalcemia is important. There are many methods to recognize hypocalcemia after TT. Clinical observation and measurement of some biochemical parameters are the worldwide used methods [4, 5]. Therefore, intact PTH (iPTH) measurement is frequently used after TT.

Low iPTH level frequently causes patients to develop hypocalcemia and hyperphosphatemia [1, 2, 6–8]. When the serum phosphorus level increases, the serum level of FGF-23, phosphaturic hormone, also increases [9–13]. FGF-23 has a decreasing effect on PTH secretion when the serum calcium level is normal. In case of hypocalcemia, FGF-23 has an increasing effect on PTH secretion [12]. FGF-23 normalize the level of phosphate by decreasing renal phosphate reabsorption, the level of the serum calcitriol and 1α-hydroxylase of 25-hydroxyvitamin D activity, and also increasing the 24(OH) ase activity. [9–11]. It is also indirectly effective in calcium regulation. When the phosphorus level returns to normal, FGF-23 levels also decreases to normal levels [9, 11, 12]. Parathyroid hormone and vitamin D control the calcium homeostasis. Moreover, they regulate phosphate level by having an impact on the kidneys and small intestines [5, 12]. In this study, we aimed to investigate the efficacy of PTH, calcium, phosphorus, vitamin D, and FGF-23 tests in detection of patients that may develop hypocalcemia after thyroidectomy.

Materials and Methods

A total of 57 patients undergoing total thyroidectomy between April 2020 and March 2022 in Dhiraj Hospital, Sumandeep Vidyapeeth , Pipariya were included in this prospective study (Table 1). Fifty-two of the patients undergoing TT were due to multinodular goiter, three of them had Graves' disease, and two had papillary thyroid cancer. Operations were performed by four experienced surgeons. All surgeons performed the same surgical protocol. TT was performed by extracapsular dissection. Recurrent laryngeal nerves were identified, isolated and carefully dissected. During the dissection, the parathyroid glands in normal localization or on the thyroid capsule were preserved and their perfusion was intact. In none of the patients, parathyroid gland auto-transplantation was required. Neck dissection was not indicated and performed in patients with papillary thyroid cancer.

The serum iPTH, total calcium, inorganic phosphorus, and vitamin D levels were measured preoperatively. Ten minutes after complete removal of the thyroid gland, PTH was measured again (intraoperative PTH: IOPTH). The relative difference in serum PTH (PTH decline) was calculated between preoperative and IOPTH: [(Preoperative PTH – IOPTH)/ Preoperative PTH] × 100. Postoperative serum PTH, calcium, phosphorus, vitamin D, and FGF-23 levels were measured 24 h after the operation.

Table 1 Characteristics of the patients

Female/male (%)	42 (73.7)/15 (26.3)
Age, years, mean (range)	49.4 (21–71)
Normocalcemia/hypocalcemia (%)	50 (87.7)/7 (12.3)

Calcium replacement was carried out in our patients when the serum calcium level was < 7.0 mg/dL. Parenteral calcium (1 or 2 g of calcium gluconate, equivalent to 90 or 180 mg elemental calcium, in 50 mL of 5% dextrose or normal saline) was administered in 10–20 min. Intravenous calcium replacement was given to the patients having clinical signs and symptoms of hypocalcemia (facial paresthesia, positive Chvostek's or Trousseau's signs, and muscular spasm) and those with a postoperative serum calcium level between 7.0 and 8.4 mg/ dL. Oral calcium (elemental calcium in doses of 1–2 g three times daily) and/or oral vitamin D (calcitrol) 1–1.5 µg/day replacement was given in patients with symptomatic hypocalcemia. Serum calcium levels of hypocalcemic patients were measured at 12-h intervals until the calcium levels became stable. Hospital stay was 1.4 days (1–4 days) in patients without hypocalcemia while patients with hypocalcemia were discharged after a mean of 4.7 days (3–6 days). Patients developing hypocalcemia were discharged with prescription of oral calcium and oral vitamin D. The patients were evaluated weekly until their serum calcium and PTH levels were within normal limits.

In our patients, the serum calcium levels improved at a mean of 4.6 weeks (2–12 weeks). None of our patients developed permanent hypocalcemia (hypocalcemia persisting for more than 6 months) or persistent hypoparathyroidism (hypoparathyroidism persisting for more than 6 months). Serum calcium levels were determined with an auto-analyzer. iPTH levels were determined in collected sample at routine hormone laboratory with electro-chemiluminescence immunoassay. Serum 1,25-dihydroxy vitamin D levels were determined with an enzyme-linked immunosorbent assay. Serum FGF-23 levels were determined with a second-generation enzyme-linked immunosorbent assay for human fibroblastic growth factor-23. Normal ranges of biochemical parameters were 12–65 pg/mL for serum parathyroid hormone, 8.4– 10.2 mg/dL for serum calcium, 2.3–4.7 mg/dL for serum phosphor, 19.2–60 pg/mL for serum 1,25-dihydroxy vitamin D, and 0–155 RU/ml for FGF-23 concentrations.

Statistical Methods

Comparisons between groups were made with Mann-Whitney U tests. Diagnostic characteristics (receiver operating characteristic curves, sensitivity, specificity, and positive and negative predictive values) were assessed to compare the diagnostic performance of the biochemical tests. Calculations were made with SPSS for Windows 17.0, using a significance level of .05.

Table 2 Characteristics of the patients with hypocalcemia

Female/Male, n (%)		7(100)/0(0)
Age, years, mean (range)		49.7 (38–56)
Pathology, *n* (%)	Nodular hyperplasia	5 (71.4)
	Hashimoto's thyroiditis	1 (14.3)
	Papillary carcinoma	1 (14.3)

Results

Total thyroidectomy was performed in all patients. Postoperative hypocalcemia developed in 7 (12.3%) of 57 patients, all were female (Table 2). None of the patients developed hypocalcemia symptoms within the first 24 h postoperatively. The serum PTH, calcium, phosphorus, and vitamin D levels at 24 h postoperatively were significantly lower in patients with hypocalcemia. The rate of PTH decline was significantly higher in these patients. The postoperative FGF-23 levels were similar between the groups (p 0.952) (Table 3).

When the biochemical parameters were evaluated, we found the sensitivity of IOPTH and postoperative PTH values as 85.7% and 85.7%, respectively. When IOPTH and postoperative calcium levels were evaluated together (IOPTH + postoperative calcium), the sensitivity was 93.5% and the specificity 75.3% (Table 4). Pathological examination revealed incidental parathyroidectomy in 9 patients.

Three of these patients had two incidental parathyroid glands excised, while six (one patient with hypocalcemia) had one incidentally excised parathyroid gland. Hypoparathyroidism was not detected in our patients.

Table 3 Diagnostic test results of the patients undergoing total thyroidectomy

	Normocalcemia ($n = 50$)	Hypocalcemia ($n = 7$)	p
Preop. PTH	106.3 (33.9–500)	64.2 (45.7–82.7)	0.210
IOPTH	58.1 (3–111)	14.3 (3–47)	0.001
PTH decline (%)	21.5	77.5	0.001
Postop. PTH	50.5 (3–151)	6.9 (3–18.6)	0.001
Postop. calcium	8.6 (6.9–10.1)	7.4 (5.8–8.5)	0.001
Postop. phosphorus	3.3 (2–7.3)	4.2 (2.5–5.7)	0.006
Preop vitamin D	43.2 (16.7–78.1)	37.5 (25.2–49.5)	0.565
Postop vitamin D	44.6 (2.5–97.1)	26.7 (9.8–54.7)	0.019
Postop. FGF-23	82.9 (8.7–382.2)	85.5 (15.2–201.1)	0.952

Preop, preoperative; *Postop*, postoperative; *vitamin D*, 1.25-dihydroxy vitamin D

Table 4 Comparison of diagnostic characteristics for hypocalcemia

	Sensitivity (%)	Specificity (%)	PPV (%)	PPV (%)
Preop. PTH	42.9	36.4	30.0	50.0
IOPTH	85.7	44.4	37.5	88.9
Postop. PTH	85.7	60.0	37.5	93.8
Postop. calcium	85.7	69.7	37.5	95.8
Postop. phosphorus	14.3	83.3	16.7	80.7
IOPTH + Postop. calcium	93.5	75.3	67.5	98.0
Postop. FGF-23	14.3	94.7	33.3	85.7

Preop, preoperative; *Postop*, postoperative; *PPV*, positive predictive value; *NPV*, negative predictive value

Discussion

Hypocalcemia is one of the most common complication after TT and may develop very early or up to 4 days after surgery [4, 5, 7, 8, 14]. Postoperative early diagnosis of biochemical and symptomatic hypocalcemia may preclude performing many biochemical tests, patient visits, and rehospitalization [15, 16]. The rate of hypocalcemia is high when the rate of PTH decline is high [17]. Rate of PTH

decline value was 77.5% in our hypocalcemic patients, while it was found to be 21.5% in normocalcemic patients.

Measurement of the serum calcium, phosphorus, PTH, and vitamin D levels is valuable in the early postoperative period [6, 8]. The decrease in the serum calcium level may be an early indicator of symptomatic hypocalcemia. Vitamin D levels were normal in all patients with hypocalcemia. Therefore, it was not found to be predictive for hypocalcemia. The highest sensitivity and positive predictive values were obtained when the IOPTH and postoperative serum calcium values were evaluated together (93.5% and 67.5%, respectively). The decrease in the serum calcium level due to hypoparathyroidism increases the serum phosphate level [1, 10]. In this situation, the level of FGF-23, a phosphate regulator, also increases. FGF-23 normalizes the phosphate level by decreasing renal phosphate reabsorption and vitamin D synthesis, and by increasing the PTH level [9, 11, 13, 18, 19].

In this study, the postoperative FGF-23 test was ineffective in revealing hypocalcemic patients (sensitivity 14.3%). Moreover, only one-third of the patients identified as hypocalcemic by the test actually had hypocalcemia (PPV = 33.3%). Although the specificity and negative predictive values of the FGF-23 test (94.7% and 85.7%, respectively) were high, this test was not found to be helpful in the determination of hypocalcemic patients postoperatively. In conclusion, the most reliable test for the detection of hypocalcemia is the evaluation of IOPTH and postoperative serum calcium levels together, while FGF-23 measurement was not diagnostic for postoperative hypocalcemia.

Compliance with Ethical Standards

All participants signed the informed consent form. Conflict of Interest The authors declare that they have no conflict of interest.

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