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Analysis of factors affecting the development of hypocalcaemia after multinodular goitre surgery

Authors' Contribution:
A – Study Design
B – Data Collection
C – Statistical Analysis
D – Data Interpretation
E – Manuscript Preparation
F – Literature Search
G – Funds Collection

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ABSTRACT:

Introduction: Thyroidectomy is a common surgery performed especially in treatment of multinodular goitre. The most common post-thyroidectomy complication is a postoperative hypocalcaemia, and the percentage of postoperative hypoparathyroidism could reach even 50%.

Tested group and methods: A forward-looking, randomized testing was done on a group of 113 women being subject to multinodular goitre surgery. In this article, we wish to present an analysis of the results obtained in the control group, focusing on the predicative factors which determine the development of postoperative hypocalcaemia.

Obtained results: The rate of postoperative biochemical hypocalcaemia development was significantly higher in the group of patients, where the preoperative calcium concentration was lower than 2,4 mmol/l. In that group, the development of biochemical hypocalcaemia was observed in 93,7% of cases (30 out of 32 patients), in comparison with 65,3% (17 out of 26) in the group of higher preoperative concentration of calcium. The highest risk of occurrence of postoperative hypocalcaemia was borne by the total thyroidectomy, while the lowest one by the subtotal thyroid lobectomy of one lobe only.

Conclusions: A higher preoperative concentration of calcium in blood serum is related to the lower rate of occurrence of postoperative biochemical hypocalcaemia. However, no such correlation was revealed in the case of postoperative symptomatic hypocalcaemia. Lack of correlation was determined between the preoperative concentration of TSH and FT4 in blood serum and the rate of occurrence of postoperative hypocalcaemia, both symptomatic and asymptomatic. The performed statistics did not reveal a relation between the postoperative hypocalcaemia and the duration of the surgery, but a significant correlation was stated with the scope of the performed surgery. Revealing a relation between the rate of occurrence of postoperative hypocalcaemia and the experience of the surgeon performing the surgery was not successful.

KEYWORDS: thyroidectomy, hypocalcemia, calcium, TSH, multinodular goiter

INTRODUCTION

As regards endocrine gland surgery, thyroid gland surgery has been most frequent for many years, and total thyroidectomy is the surgical treatment of choice for multinodular goitre [1,2]. The most common complication of thyroidectomy is postoperative hypocalcaemia, which can be temporary or permanent [3-7]. The frequency of temporary hypocalcaemia varies between 6.9% and 83%, depending of the study. The frequency of permanent hypocalcaemia ranges between 0.4% and 33% [1,8]. Postoperative hypocalcaemia is a reason for prolonged hospitalization, which generates treatment costs and deteriorates the patient's quality of life due to the necessity to supplement calcium and perform regular outpatient checks [9,10]. Some of the risk factors for the development of hypocalcaemia after thyroid gland surgery are commonly recognized and include the scope of surgery, extent of post-operative injury, accidental removal of parathyroid glands, and hungry bone syndrome [11,14]. The following factors may also have an influence on the frequency of postoperative hypoparathyroidism: operator experience, duration of surgery, lymphadenectomy in the neck, substernal goitre, and cancer [15]. Studies performed in recent years have also revealed a relation between preoperative serum concentration of vitamin D3 and the occurrence of postoperative temporary hypocalcaemia [16,17]. Moreover, early postoperative supplementation with calcium and vitamin D3 effectively prevents this complication [18-20].

TESTED GROUP AND METHODS

In the General Surgical Ward of the Beskid Oncology Centre of the City Hospital in Bielsko-Biała, Poland, a prospective study has been performed to determine the effect of preoperative oral vitamin D3 supplementation on the occurrence of postoperative hypocalcaemia in female patients who undergo thyroidectomy for multinodular goitre. The occurrence of symptomatic and asymptomatic hypocalcaemia has been noted (a decrease in total serum calcium concentration below 2.15 mmol/l). In order to create a homogenous study sample, from approximately 160 patients who are annually operated on due to thyroid gland conditions, only women were included. The available literature on the relation of gender with the risk of postoperative hypocalcaemia is ambiguous, although some authors indicate a higher frequency of hypocalcaemia in women [21]. The remaining inclusion criteria were as follows: age of 25-70 years, diagnosis of thyroid multinodular goitre, clinical and biochemical euthyreosis, lack of hormonal contraindications to surgery, consent to proposed treatment, and consent to postoperative observation.

The exclusion criteria were as follows: substernal goitre, re-operation (history of thyroidectomy), suspicion of cancer based on FNAB, or significant general medical contraindications (ASA >3).

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Every patient to be operated on was assigned to one of two groups, based on a unique sequence of random numbers generated beforehand with the Research Randomizer software. Patients with even numbers were assigned to the experimental group, while those with odd numbers were assigned to the control group. Patients in the experimental group received oral supplementation with vitamin D3 for two months prior to surgery.

To date, 113 women have been enrolled (55 patients in the experimental group and 58 in the control group).

We wish to present the results that have been obtained in the control group and focus on factors that predict the development of postoperative hypocalcaemia. We report the results obtained only from the control group, because vitamin D3 supplementation could be a confounding factor. The effect of oral vitamin D3 supplementation on the frequency of postoperative hypocalcaemia will be presented in a separate publication, once the assumed number of participants in the experimental group has been reached.

Asymptomatic hypocalcaemia (biochemical hypocalcaemia) was defined as serum total calcium concentration lower than 2.15 mmol/l (Ca< 2.15 mmol/l). Symptomatic hypocalcaemia was noted when there was tetany or at least one of its equivalents such as paraesthesia, coronary artery spasm, abdominal, cerebral, or peripheral vasoconstriction, laryngospasm, bronchospasm, eyelid muscle contractions, photophobia, and double vision.

During the first three days after surgery, the patients were monitored for postoperative complications, and especially for symptomatic hypocalcaemia. On the second day after surgery, regardless of the presence of symptoms, total serum calcium concentration was determined in every patient. In the case of symptomatic hypocalcaemia, the concentration of total serum calcium was determined immediately and then monitored every day until a relative stabilization was observed.

In the case of asymptomatic hypocalcaemia, oral calcium supplementation (calcium carbonate, 2000 – 6000 mg/day) in combination with vitamin D3 (alfacalcidol 1 – 2 mcg/day) was instituted. In the case of tetany or its equivalents, intravenous calcium was administered (potassium chloride of 1500 - 3000 mg), and then oral supplementation was continued.

As regard the statistical analysis, Pearson's correlation coefficient (PCC, r) was used for normally distributed data, and Spearman's rank correlation coefficient (R) was used otherwise. We also used the Fisher's exact test (one-tailed) and the Pearson's chi-squared test (one-tailed). Statistical significance was set at $p \leq 0.05$. Results

Among 58 patients in this study, 49 had hypocalcaemia (84.4%), of whom 16 (27.6%) were symptomatic and 33 (56.9%) asymptomatic. In each case of symptomatic hypocalcaemia, mild to moderate paraesthesia, a sensation of numbness and tingling in fingers, toes, mouth, and tongue, was observed. There were no instances of laryngospasm, and none of the patients reported disorders of the heart rhythm. The symptoms of hypocalcaemia occurred in 4 patients on the day of surgery, in another 7 patients during the first 24 hours after surgery, and in another 5 patients 24 hours after surgery.

Calcium concentrations varied between 2.16 and 2.58 mmol/l (average 2.37 mmol/l) before surgery, and between 1.1 and 2.33 mmol/l (average 2.03 mmol/l) on the second day after surgery. The concentration of total calcium after surgery had a weak positive correlation with the concentration of calcium before surgery (r=0.255), and the average decrease in calcium concentration was 0.32 mmol/l.

The rate of postoperative biochemical hypocalcaemia was significantly higher in the group of patients with preoperative calcium concentrations lower than 2.4 mmol/l (Fisher's exact test, p=0.0081, one-tailed). In that group, biochemical hypocalcaemia was observed in 93.7% of cases (30 out of 32 patients), in comparison to 65.3% (17 out of 26) among the remaining patients. However, no such correlation was revealed in the case of postoperative symptomatic hypocalcaemia (p=1). Symptomatic hypocalcaemia developed in 8.1% of patients (9 out of 32) with preoperative calcium concentration <2.4 mmol/l, and in 26.9% of patients (7 out of 26) with calcium concentrations above 2.4 mmol/l. The occurrence of postoperative hypocal-

Tab. I. Concentrations of TSH and FT4.

	Minimum concentration	Maximum concentration	Mean concentration	Normal range	Standard deviation
TSH	0,01	3,13	1,19	0,27 - 4,20 uU/ml	0,75
FT4	0,84	1,78	1,26	0,93 - 1,71 ng/dl	0,21

Tab. II. Scope and duration of surgery.

	NUMBER OF CASES	ASYMPTOMATIC HYPOCALCAEMIA	SYMPTOMATIC HYPOCALCAEMIA	AVERAGE TIME OF SURGERY [MIN]
Total thyroidectomy	21	10	11	76
Total thyroid lobectomy of one lobe and subtotal of the other lobe	19	13	3	75
Subtotal thyroid lobectomy of both lobes	12	6	1	75
Total thyroid lobectomy of one lobe only	4	2	0	55
Subtotal thyroid lobectomy of one lobe only	2	0	1	64

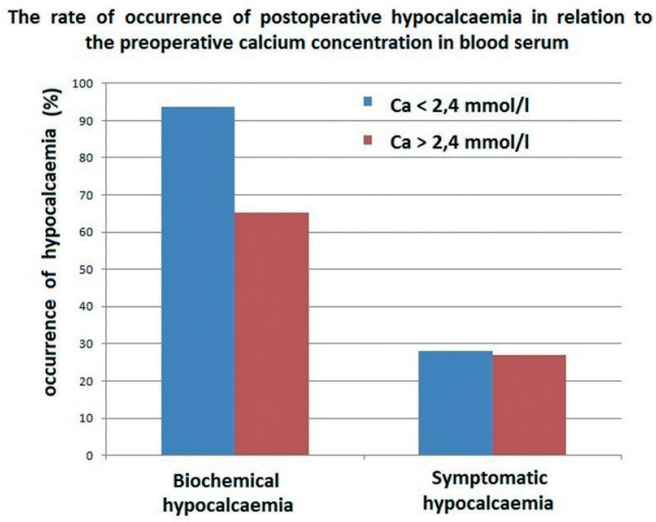

Fig. 1. Occurrence of postoperative hypocalcaemia in relation to preoperative serum calcium concentration.

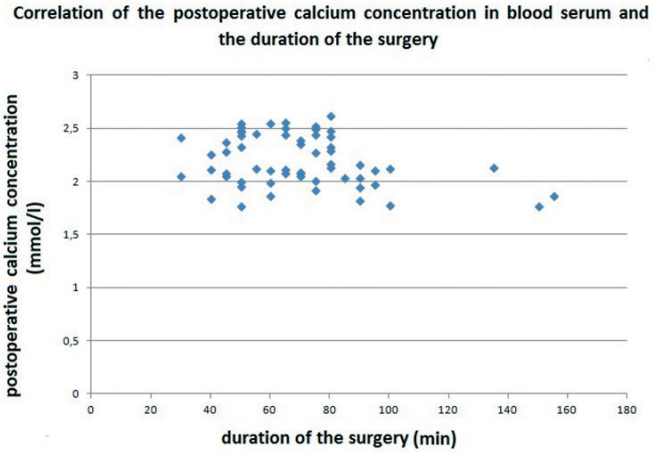

Fig. 2. Correlation between postoperative serum calcium concentration and the duration of the surgery.

caemia in relation to the preoperative serum calcium concentration is shown in Figure 1.

As regards the thyroid-stimulating hormone (TSH), no statistically significant correlation was observed between its preoperative concentration and the occurrence of postoperative biochemical hypocalcaemia (serum calcium concentration < 2.15 mmol/l). Biochemical hypocalcaemia developed in 81.4% of patients (22 out of 27) with TSH concentrations lower than 1.0 uU/ml, and in 67.7% of patients (21 out of 31) with TSH concentrations above 1.0 uU/ml (p=0.36). No correlation was observed between preoperative TSH concentrations and the development of postoperative symptomatic hypocalcaemia (p=1).

There was no correlation between the occurrence of postoperative hypocalcaemia, both biochemical and symptomatic, and preoperative concentrations of free thyroxin (FT4). Concentrations of TSH and FT4 are presented in Table 1.

It is commonly accepted that the scope of surgery, and thus the scope of operative injury, affects function of the parathyroid glands. The following procedures were performed among the analysed patients: 21 cases of total thyroidectomy, 19 cases of total thyroid lobectomy of one lobe with partial lobectomy of the second lobe, 12 cases of subtotal thyroidectomy, 4 cases of total thyroid lobectomy of one lobe without dissecting the other lobe, and 2 cases of partial lobotomy of one lobe only.

In the analysed groups, surgery duration ranged from 30 to 155 minutes (average 74.4 minutes) and was not significantly related to the scope of surgery. The shortest surgery duration was noted for total thyroid lobectomy of one lobe (30 minutes) and the longest for total thyroidectomy (155 minutes).

The scope of surgery, occurrence of postoperative hypocalcaemia, and the average duration of surgery are presented in Table 2.

Based on the Pearson's chi-squared test, there was a statistically significant association between the scope of surgery and the occurrence of postoperative hypocalcaemia (p=0.012). The highest risk of postoperative hypocalcaemia was associated with total thyroidectomy, while the lowest risk was associated with subtotal thyroid lobectomy of one lobe only. There was no correlation between the duration of surgery and the calcium concentration on the second day after surgery (R=-0.126 ; p=0.47). The correlation between the postoperative calcium concentration and surgery duration is shown in Figure 2.

In addition, the occurrence of postoperative hypocalcaemia was assessed with respect to operator experience. To that end, surgeons were divided into two groups: group "A" consisted of surgeons in training (residents), and group "B" consisted of surgeons with more than 10 years of experience. The list of performed procedures and their results are presented in Table 3. Based on the Fisher's exact test, there was no significant association between operator experience and the occurrence of postoperative biochemical hypocalcaemia (p=0.078, one-tailed).

CONCLUSIONS

Higher preoperative concentrations of serum calcium are related to a rarer occurrence of postoperative biochemical hypocalcaemia. However, no such correlation was revealed in the case of postoperative symptomatic hypocalcaemia. There was no correlation between preoperative serum concentrations of TSH and FT4 and the occurrence of postoperative hypocalcaemia, both symptomatic and asymptomatic. There was no relation between postoperative hypocalcaemia and the duration of surgery, but a significant correlation was observed with the scope of surgery. There was no relation between the occurrence of postoperative hypocalcaemia and operator experience.

DISCUSSION

Although in our patients postoperative hypocalcaemia was common, symptoms of hypocalcaemia resolved with treatment (as described above). Two weeks after surgery, there was a gradual increase in serum calcium concentration, and supplementation

was decreased. However, 11 patients (18.9%) still needed further calcium and vitamin D3 supplementation. After discharge, none of the patients reported recurrence of any hypocalcaemia symptoms. The patients were followed-up until total normalization of serum calcium was observed, after which administration of oral calcium preparations was discontinued. Is should be emphasized that no case of permanent hypocalcaemia was noted, and all patients finished calcium and vitamin D3 supplementation within 2 months after surgery.

Our results show that higher preoperative concentrations of serum calcium are related to higher calcium concentrations after surgery, which lowers the rate of postoperative hypocalcaemia. This observation is of value and might be used in order to prevent postoperative hypocalcaemia in patients who undergo thyroidectomy.

To date, our data have not revealed any correlation between the occurrence of postoperative hypocalcaemia and preoperative concentrations of TSH and FT4, although some authors reported a correlation between serum concentrations of TSH and calcium [23,24]. Based on previous research, lower calcium concentrations were observed in hypothyroidism, whereby TSH concentrations are elevated.

Interestingly, we did not observe any relation between postoperative hypocalcaemia and the duration of surgery or operator experience; however, postoperative hypocalcaemia correlated with the scope of surgery. This might be due to a small sample size or to a lack of significant differences in performance between surgeons with different experience. The latter statement may be confirmed by the fact that parathyroid glands were not removed inadvertently with the thyroid gland, as observed on histology. In addition, human factor may be of significance, as the person who manages the ward usually assigns less experienced surgeons to simpler cases and provides them with assistance of more experienced surgeons.

Tab. III. List of surgeons

	GRUPA A	GRUPA B
Total number of surgeries	35	23
Average time of surgery [min]	77	74
Number of hypocalcaemia cases	28 (80%)	13 (56,5%)
Detailed number of performed surgeries		
Total thyroidectomy	16 (45,7%)	9 (39,1%)
Total thyroid lobectomy of one lobe and subtotal of the other lobe	10 (28,5%)	7 (30,4%)
Subtotal thyroid lobectomy of both lobes	17 (17,1%)	2 (8,7%)
Total thyroid lobectomy of one lobe only	2 (5,7%)	5 (21,7%)
Subtotal thyroid lobectomy of one lobe only	1 (2,8%)	0

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