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PREDICTIVE VALUE OF SERIAL CALCIUM MEASUREMENTS FOR OCCURRENCE OF HYPOCALCAEMIA AFTER THYROID SURGERY

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The occurrence of hypocalcemia is an important and frequent complication of thyroidectomy that occurs in up to 75% of all surgeries. The value of serial measurement of serum calcium in postoperative period has a questionable validity. We aimed to evaluate the value of serial calcium measurements and other clinical and biochemical factors as predictors for occurrence of hypocalcaemia.

We prospectively evaluated 50 patients subjected to thyroid surgery due to various indications during the year 2011. Predictive values of serial calcium measurements were evaluated by using Receiver Operating Characteristics (ROC) analysis.

We recruited 50 patients with average age (SD) of 49.32 (12.15) years, spanning from 18 to 72 years. There were 38 (76%) female patients with women to men ratio of 3.17 to 1. There were 13 (26%) patients with the occurrence of hypocalcemia, out of which the most had temporary hypocalcemia (11; 22%). when comparing malignancy (8/17; 47.1%) vs. other reasons for surgery (5/33;15.15%), there were proportionally more patients with hypocalcaemia, among patients referred for surgery due to thyroid malignancy (X2=4.39; df=1; p=0.036). We compared predictive value of each particular calcium measurement for prediction of occurrence of hypocalcaemia and there was no statistical difference between AUROCs. A detailed ROC analysis for calcium measurement on day 2 was performed with the best performing threshold value of calcium of 1.95 with sensitivity of 70%, specificity of 97% and positive and negative predictive value of 90%.

Serial measurement of calcium in postoperative period after thyroid surgery is not necessary and that measurement on second day after surgery is sufficient for predicting the occurrence of hypocalcaemia. Values of calcium measured 6 hours after the surgery may be used as an early and less precise predictor for occurrence of hypocalcaemia.

Keywords: calcium, hypocalcaemia, thyroid surgery, thyroidectomy

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Competing interests
The authors declare no competing interests.

INTRODUCTION

The occurrence of hypocalcemia is an important and frequent complication of thyroidectomy that occurs in up to 75% of all surgeries.[1-4] However, the frequency of hypocalcaemia shows a remarkable variability, mainly due to differences in definition of hypocalcaemia and partially due to variance in laboratory ranges of normal calcium levels. It is hypothesized that hypocalcaemia occurs due to combination of one or more various factors of which injury and/or removal of parathyroid glands seems to be the most likely cause.[1, 3, 5] This is supported by the fact that hypocalcaemia rarely occurs in case of partial thyroidectomia and hardly ever with thyroid lobectomy.

Hypocalcaemia after thyroid surgery is usually a temporary phenomenon, but there is a small percentage of patients with permanent hypocalcaemia.[3, 6] This is a potentially hazardous complication that requires prompt treatment and supplementation which is why many surgeons routinely check for calcium levels in serial measurements. This is a practice of dubious validity which has been questioned in literature. [7] Several factors have been evaluated in terms of their predictive power for development of hypocalcaemia after thyroid surgery, however without general agreement. [3, 6, 8]

Therefore, we aimed to determine the frequency of occurrence of transient and permanent hypocalcaemia after thyroid surgery, and to evaluate the value of serial calcium measurements and other clinical and biochemical factors as predictors of occurrence for hypocalcaemia.

PATIENT AND METHODS

We prospectively evaluated 50 patients subjected to thyroid surgery due to various indications during the year 2011. We gathered data from hospital records at the Department of ENT, Department of Nuclear

Medicine and Department of Pathology at the University Clinical Centre Tuzla.

We recorded information regarding the type of surgery and indication for surgery, age, gender, presence of recurring goitre, size and weight of the removed gland, histologic diagnosis, histologic proof of presence of parathyroid tissue, presence of perioperative complications. Serial measurements of calcium were taken at 24 hour before, 6 hours after the surgical procedure and from postoperative day 1 to 3, on day 10 and 6 weeks after the procedure. If patient had calcium level below the lower limit of normal a supplementation was administered in the form of calcium gluconate souluton 1 to 2 times per day intravenously.

Primary outcome was defined as presence of either transient or permanent hypocalcaemia while secondary outcome was defined as occurrence of postoperative complications.

STATISTICAL ANALYSIS

We performed statistical analysis with statistical package SPSS 18.0 (SPSS Inc, Chichago, IL, USA). Associations between categorical variables were tested with the chi-squared test whereas the Student's t-test was used for comparison of continuous variables. Univariate binomial logistic regression analysis was used to test predictive potential of each parameter of interest for presence of hypocalcaemia. Furthermore, each parameter found to be significant predictor on univariate analysis was entered in multivariate analysis.

Statistical significance was considered to be any test with a $P < 0.05$.

RESULTS

We recruited 50 patients with average age (SD) of 49.32 (12.15) years, spanning from 18 to 72 years. There were 38 (76%) female patients with women to men ratio of 3.17 to 1.

Baseline characteristics of patients are presented in table 1.

Serum calcium levels were serially measured - the recorded values are presented in table 2. There were 13 (26%) patients with the occurrence of hypocalcemia, out of which the most had temporary hypocalcemia (11; 22%). Regarding the physical signs of hypocalcemia, there was no any occurrence of heart arrhythmias and laryngospasm, while Chvostek sign was recorded in 2 patients (4%) and paresthesias and tetany were observed in 13 cases, each (26%).

There were no differences in occurrence of postoperative hypocalcaemia in regards to the gender of the patients (F 12/38; 31.58% vs. M 1/12; 8.33%), nor in regards to the indication for operative treatment ($p>0.05$). However, when comparing malignancy (8/17; 47.1%) vs. other reasons for surgery (5/33;15.15%), there were proportionally more patients with hypocalcaemia, among patients referred for surgery due to thyroid malignancy ($X2=4.39$; $df=1$; $p=0.036$).

There were significantly more patients (Fisher's test; $p=0.009$) with hypocalcaemia within the group of patients that underwent total (11/26; 42.31%) than those that were subjected to partial thyroidectomy (2/24; 8.33%).

The comparison of mean volume and weight of extirpated thyroid gland tissue is presented on table 3. There were no statistically significant differences between patients with or without hypocalcaemia, although there was tendency for patients with hypocalcaemia to have both larger volume and mass of thyroid tissue.

Table 1: Baseline characteristics of patients

Parameter		
Gender (N=50)	Females 38; 76%	Males 12; 24%
Indications for surgery (N=50)	Goitre 28; 56% Cancer 17; 34%	Graves disease 2; 4% Re-operation 3; 6%
Extent of surgery (N=50)	Total 25; 50% Partial 24; 48%	Subtotal 1; 2%
Lobectomy (N=24)	Right lobe 14; 58%	Left lobe10; 42%
Neck dissection (N=50)	Without 46; 92%	With 4; 8%
Histological diagnosis (N=50)	Goitre 24; 48% Tumour 21; 42%	Other 5; 10%
Histological proof of presence of parathyroid gland tissue (N=50)	Yes 2; 4%	No 48; 96%
Postoperative complications (N=50)	Yes 18; 36%	No 32; 64%
Postoperative haemathoma (N=50)	Yes 2; 4%	No 48; 96%
Postoperative bleeding (N=50)	Yes 2; 4%	No 48; 96%
Recurrent nerve paralysis (N=50)	No 46; 92% Transient 1; 2%	Permanent 3; 6%
Right lobe volume (ml) (N=39)	Mean (SD) 40.91 (42.2)	Range 4.23 - 222.77
Left lobe volume (ml) (N=35)	Mean (SD) 18.65 (19.03)	Range 0.26-92.58
Total volume (ml) (N=50)	Mean (SD) 44.96 (45.06)	Range 0.26-232.29
Weight (g) (N=50)	Mean (SD) 45.50 (43.33)	Range 7.30-204.20

Table 2: Serial measurements of serum calcium

	Mean	SD	Minimum	Maximum
Ca before surgery	2.31	0.15	2.11	2.82
Ca 6 hours after surgery	2.08	0.18	1.50	2.41
Ca 1 day after surgery	2.10	0.21	1.56	2.49
Ca 2 days after surgery	2.10	0.19	1.50	2.51
Ca 3 days after surgery	2.12	0.26	1.16	2.53
Ca on first follow-up	2.09	0.39	1.10	2.80
Ca 6 after surgery	2.27	0.13	1.69	2.53

SD-standard deviation

We compared values of serial calcium measurements between groups of patients with and without hypocalcaemia and found statistically lower values within patients with hypocalcaemia in all measurements except at the preoperative one ($p<0.05$). Graphical representation of serial measurements in both groups is presented on figure 1.

Table 3: Comparison of volume and mass of extirpated thyroid tissue between patients with and without occurrence of postoperative hypocalcaemia

	Hypocalcaemia	Mean	SD	p-value
Total volume	No	39.01	35.56	0.116
	Yes	61.91	63.83	
Mass	No	39.24	31.83	0.085
	Yes	63.33	64.52	

SD-standard deviation

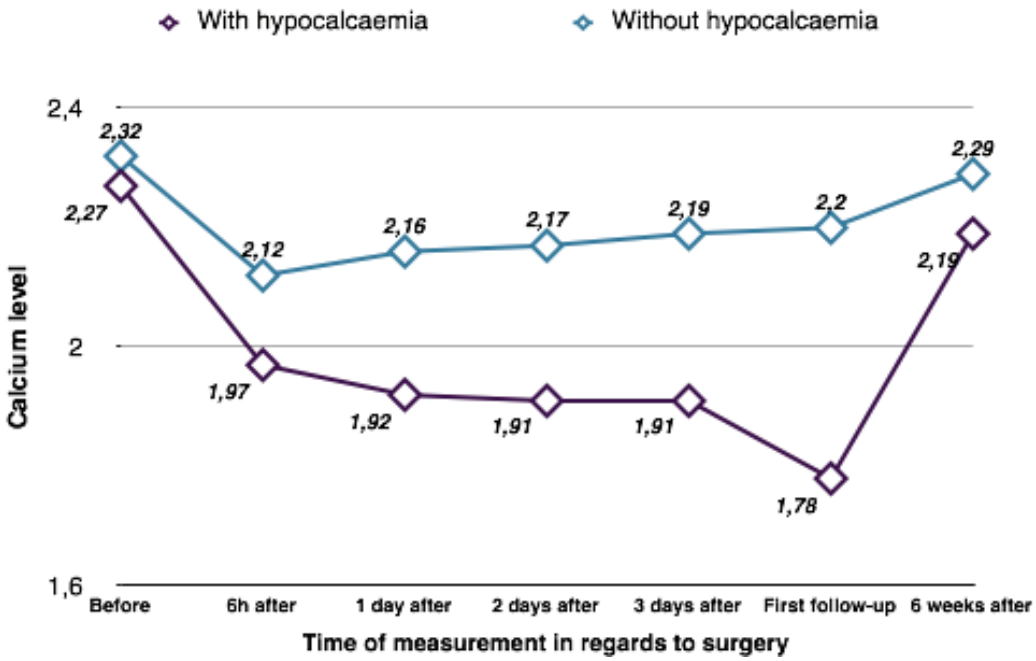

Figure 1: Serial measurements of serum calcium in groups of patients with and without hypocalcaemia

We compared predictive value of each particular calcium measurement for prediction of occurrence of hypocalcaemia by using pairwise comparison of areas under the ROC curves (AUROC). The analysis is presented in table 4 and there was no statistical difference between AUROCs.

Table 4: Comparison of Areas Under the ROC Curves for serial calcium measurements for prediction of occurrence of hypocalcaemia after thyroid surgery

Measurements	AUROC	p-value	95% confidence interval (CI)	
			Lower limit	Upper limit
Ca 6 hours after surgery	0.761	0.006	0.597	0.924
Ca 1 day after surgery	0.822	0.001	0.681	0.963
Ca 2 days after surgery	0.838	0.000	0.703	0.973
Ca 3 days after surgery	0.825	0.001	0.698	0.953
Ca on first follow-up	0.860	0.000	0.759	0.960
Ca 6 weeks after surgery	0.684	0.050	0.501	0.867

We performed a detailed ROC analysis for calcium measurement on day 2. The AUROC is presented in table 4. The best performing threshold value of calcium was 1.95 with sensitivity of 70%, specificity of 97% and positive and negative predictive of 90%. For this population positive likelihood ration was 25.62 and overall accuracy was 90%.

DISCUSSION

The pronounced domination of female patients in our sample is a result of a very well determined fact that females more frequently have thyroid pathology.[9, 10] According to results of a study conducted by Canadian authors females have an increased risk of temporary hypocalcaemia after thyroid surgery, while other report suggests that there is also an increased risk of permanent hypocalcaemia among females as well.[11, 12]

The same group of authors extensively discussed possible reasons for gender difference and they concluded that specific mechanisms can only be inferred.[12] There are several possible theories - possible effect of sex steroids on parathyroid hormone secretion, differences in anatomic and morphologic peculiarities of the male and female parathyroid glands (higher weight in men and possible difference in composition of glands). Each of the mentioned possibilities is very far-fetched and this whole phenomenon demands further investigation.

We did not have statistically significant difference in the occurrence of hypocalcaemia among genders, although there was an obvious dominance of hypocalcaemia among female patients. Del Rio and al. suggested that in patients undergoing thyroid surgery due to benign thyroid diseases, the female gender is the only established risk factor for hypocalcaemia.[13]

Most of the patients in our sample were operated due to goitre or malignoma with more patients with hypocalcaemia among patients treated for thyroid malignoma. Röher and al. Determined that the main risk factors for occurrence of hypocalcaemia are Graves disease, malignancy and type of surgery.[14] Our patients also had hypocalcaemia more often when subjected to total thyroidectomy. This is probably the result of the higher risk for lesion of parathyroid glands - proportional to the extent of the surgery.[1, 3, 15]

The assessed volume of thyroid gland represents an important factor for occurrence of all types of postoperative complications after thyroid surgery.[16] In patients with smaller volume of thyroid gland there is an increased risk for hypocalcaemia, while in more voluminous thyroid glands a risk for a lesion of recurrent nerve or bleeding becomes a more prominent issue. Our patient had tendency to have both larger volume and mass in subgroup of patients with hypocalcaemia, although without statistical significance.

The lack of clear consensus regarding the definition of temporary hypocalcaemia impairs reliable comparison of incidence of this problem among published reports. There are authors that consider asymptomatic hypocalcaemia, while others take into account only symptomatic hypocalacaemia. [17, 18] There are also surgeons that routinely administer calcium after total thyroidectomy which may mask the true incidence of hypocalcaemia and there are also discrepancies in techniques of calcium measurement among various reports.[19] This is why the incidence of postoperative hypocalcaemia is highly variable among different reports and ranges between 0.5% and 75%.[1-4, 8, 11] Our results fit within this range.

We compared ROC values of different serial measurements of calcium for prediction of occurrence of hypocalcaemia and did not find any significant difference in predictive power of each particular measurement, excluding preoperative values. This supports our hypothesis that serial measurements are unnecessary and therefore we arbitrarily used value measured on second postoperative day in further analysis, due to highest ROC value (highest accuracy) and obvious practical reasons. Our results suggest that patient with calcium value lower than 1.95 has 90% chance for developing hypocalcaemia.

Studies dealing with this issue report contradictory findings. A South American study suggested that calcium measurement on day 1 and 2 after the surgery are not sufficient for prediction of hypocalcaemia [20] while other group of authors emphasise the value of calcium measurement on 6 hours and 1 day following the surgery due to slope of curve representing the serial calcium measurements.[7] Our results may confirm this since values of calcium hardly show any variation after 6 hours measuremnt in patients with hypocalcaemia (figure 1). Bearing in mind that AUROC value for this particular measurement is only slightly lower, one

may argue that this measurement may also be used as a less precise but early predictor of developing hypocalcaemia.

In conclusion, we propose that serial measurement of calcium in postoperative period after thyroid surgery is not necessary and that measurement on second day after surgery is sufficient for predicting the occurrence of hypocalcaemia. Values of calcium measured 6 hours after the surgery may be used as an early and less precise predictor for occurrence of hypocalcaemia. Larger volume of thyroid gland, total thyroidectomy and female gender may contribute to this phenomenon.

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