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Impact of intraoperative calcium injection for prophylaxis against Hypocalcemia after Total Thyroidectomy for Benign Thyroid Disease

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ABSTRACT

Background:
Hypocalcemia, the most common complication of total thyroidectomy, is a transient condition in up to 27% of patients and a permanent condition in 1%. The present study was conducted to assess whether intra-operative parenteral administration of 10 ml calcium gluconate (500 mg of calcium) is beneficial in preventing post-operative hypocalcemia after total thyroidectomy for benign thyroid disease.
Patients and Methods:
This study included 100 consecutive normocalcemic patients with benign thyroid disease who were candidates for total thyroidectomy. Patients included 73 females and 27 males. Their ages ranged from 18 to 55 years, with a mean of 35.7±9.5 years and were randomized using the closed envelope method into two groups of 50 patients each. Group I patients received intra-operative intravenous (IV) injection of 10 ml calcium gluconate containing 500 mg of calcium, while Group II patients did not and served as controls. Serum calcium level was measured pre-operatively, at 6 hours and at 5 days post-operatively.
Results:
The incidence of post-operative hypocalcemia was significantly lower in Group I than in Group II patients (38% versus 62%, respectively). Eighteen patients (36%) in Group I suffered from mild hypocalcemia manifested with perioral numbness, tingling and positive Chvostek's sign as compared to 28 (56%) in Group II (X^2=5.944, P=0.047).
Conclusion:
From this study it may be concluded that prophylactic IV injection of calcium gluconate during total thyroidectomy is effective in lowering the risk of post-operative symptomatic hypocalcemia.

Kew word: Hypocalcemia, thyroidectomy, benign thyroid disease

INTRODUCTION

The normal parathyroid glands are flat, ovoid, and red-brown to yellow in color. They are approximately 5 × 3 × 1 mm in size and weigh between 30 and 50 mg each. The lower glands are usually larger than the upper glands. [1] The superior glands are most often embedded in the fat on the posterior surface of the upper thyroid lobe near the site where the recurrent laryngeal nerve (RLN) enters the larynx. The inferior glands are usually more ventral and lie close to or within the portion of the thymus gland that extends from the inferior pole of the thyroid gland into the chest. [1]

In the absence of thyroid nodules, high-resolution ultrasound (US) can be a useful tool for localization of a parathyroid adenoma prior to surgery. Scintigraphy with technetium-99m-Sestamibi and US are needed when the patient has thyroid abnormalities in addition to hyperparathyroidism.[2] The blood supply to the superior parathyroids usually originates from the inferior thyroid artery (ITA), and occasionally from anastomosis of the inferior and superior thyroid arteries. The blood supply to the inferior parathyroids is from ITA (90.3%) and thyroidea ima artery in less than 10%. [3]

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In blood, approximately 50% of total calcium is bound to proteins, mainly albumin and globulins, while the remaining 50% is free (ionized). The ionized calcium concentration in serum is approximately 5 mg/dL, and it is the fraction that is biologically active and tightly controlled by hormonal mechanisms.[4] Extracellular calcium is important for excitation–contraction coupling in muscle tissues, synaptic transmission in the nervous system, coagulation, and secretion of other hormones. Intracellular calcium is an important second messenger regulating cell division, motility, membrane trafficking, and secretion.[5] Normal plasma levels of total calcium vary between laboratories, but the range of total calcium is usually between 8.5 and 10.5 mg/dL.[6]

The cause of post-operative hypocalcemia is multifactorial; it can be caused by injury, inadvertent removal, or devascularization of the parathyroid glands.[7] The incidence of post-operative hypoparathyroidism is also associated with the number of ligatures placed in close approximation to the parathyroid gland.[8] Other causes include the hungry bone syndrome resulting in low serum calcium levels as remineralization occurs.[9] The hallmark of acute hypocalcemia is neuromuscular irritability. Patients often complain of numbness and tingling in their fingertips, toes, and the perioral region. Paresthesias of the extremities may occur, along with fatigue and anxiety. Muscle cramps can be very painful and progress to carpal spasm. Hypocalcemia can present dramatically as tetany, seizures, and altered mental status.[10]

Chronic hypocalcemia may have a different presentation. Patients may develop calcification of the basal ganglia and extrapyramidal neurologic symptoms; grand mal, petit mal, or focal seizures have been described. Subscapular cataracts may occur. Paravertebral ligamentous ossification has been noted in 50% of cases with hypoparathyroidism and antalgic gait may be noted.[11] To prevent such a complication preservation of the parathyroids in-situ through meticulous dissection without jeopardizing their blood supply should be exercised, or autotransplantation of parathyroid glands inadvertently resected or devascularized during thyroidectomy.[12]

SUBJECTS AND METHODS

Study Population:

The present controlled randomized study was conducted on 100 patients who were admitted to the surgical department at the Alexandria University Main hospital, Head and Neck and Endocrine Surgery Unit (HNESU), Alexandria University, Egypt. Patients were randomized using the closed envelope method into two groups of 50 patients each. Group I patients received intra-operative intravenous (IV) injection of10 ml of calcium gluconate containing 500 mg of calcium, while Group II patients did not and served as controls. Serum calcium level was measured pre-operatively, and at 6 hours and 5 days post-operatively. There were 73 females patients and 27 males patients included in the study. Their ages ranged from 18 to 55 years, with a mean of 35.7±9.5 years. All patients had benign thyroid disease requiring total thyroidectomy. Patients with pre-existing hypocalcemia or received calcium supplementation, those who had Besthesda IV, V and VI lesions by fine needle aspiration cytology (FNAC), as well as patients who required completion thyroidectomy or concurrent lymph node dissection were all excluded from the study.

Pre-operative Assessment:

All patients were subjected to thorough history-taking and complete physical examination. Laboratory investigations included thyroid function tests (TSH, FT_3, FT_4) and serum calcium level; total and ionized. Imaging studies included neck ultrasound (US) and Plain X-ray chest for all patients. Fine needle aspiration cytology was also performed for all patients.

Operative Technique:

All patients in group I were injected during induction of anaethesia with IV 10% calcium gluconate. Conventional thyroidectomy was performed for all patients via a transverse collar incision with the patient under general anesthesia. Careful dissection along the thyroid capsule was performed in an attempt at identifying and preserving the parathyroid glands along with their vascular supply as well as the recurrent and external laryngeal nerves.

Post-operative Assessment:

Post-operative histopathology of the submitted thyroidectomy specimen was done, signs and symptoms of hypocalcemia were assessed, and serum total and ionized calcium were measured at 6 hours and 5 days post-operatively.

Statistical Analysis:

Data were analyzed using the SPSS software package version 20.0 (Prentice Hall, Chicago, IL, USA). Qualitative data were described using number and percent. Quantitative data were compared using the student t test. Comparison between categorical variables of the two groups was done using the Chi-square (X^2) test. When more than 20% of the cells have expected count less than 5, correction for Chi-square was conducted using Fisher Exact test or Monte Carlo correlation (MC). A “p” value of <0.05 was considered to be statistically significant. Agreement of the different predictives with the outcome was used and was expressed in sensitivity and specificity.

RESULTS

As seen in Table-1, there was no significant difference between the two groups regarding gender, age, and clinical presentation. Moreover, patients in the two groups had similar US and thyroid function as well as Besthesda grades on FNAC. Post-operatively, the most common diagnosis was simple multinodular goiter (MNG)

Table-1. Comparison of pre-operative data between the two studied groups.

Demographic data	Group I (n=50)		Group II (n=50)		Test of significance	p
	N	%	N	%		
Gender						
- Male	15	30.0	12	24.0	χ^2=0.457	0.499
- Female	35	70.0	38	76.0		
Age (years)						
- Min – Max	18 – 50		20 – 55		t=1.780	0.078
- Mean ± SD	34.2 ± 9.6		37.6 ± 9.5			
Clinical picture						
- Neck swelling	30	60.0	35	70.0	χ2=1.319	0.560
- Neck swelling with toxic symptoms	17	34.0	12	24.0		
- Neck swelling with pressure symptoms	3	6.0	3	6.0		
US findings						
- MNG	29	58.0	34	68.0	χ2=2.485	0.684
- Toxic nodular goiter	12	24.0	10	20.0		
- Diffuse toxic goiter	5	10.0	2	4.0		
- MNG with lymph node	2	4.0	1	2.0		
- MNG with RSE	2	4.0	3	6.0		
Thyroid function						
- Euthyroid state	33	66.0	38	76.0	χ2=1.214	0.271
- Controlled toxic	17	34.0	12	24.0		
Besthesda classification						
- II	48	96.0	47	94.0	χ2=0.211	1.000
- III	2	4.0	3	6.0		

MNG: Multinodular goiter, RSE:Retrosternal extension

(85%), followed by Graves' disease (7%). There was no significant difference between the two groups regarding histopathological diagnosis (X^2 =2.485, p= 0.684). The incidence of manifestations of post-operative hypocalcemia (mild or severe) in Group I patients was significantly lower than in Group II patients (38%, versus 62% respectively), as shown in Table-2 revealing the significant effect of intra-operative calcium injection in reducing post-operative hypocalcemic manifestations.

Table-2. Comparison of the severity of post-operative hypocalcemia between the studied groups

Manifestations	Group I (n=50)		Group II (n=50)		χ^2	p
	N	%	N	%		
No hypocalcemia	31	62.0	19	38.0	5.944*	0.047*
Mild hypocalcemia	18	36.0	28	56.0		
Severe hypocalcemia (tetany)	1	2.0	3	6.0		

Table-3 shows that Group I patients had significantly higher levels of post-operative serum calcium than Group II after one and five days. This reflects the effect of calcium prophylaxis during induction of anesthesia on increasing post-operative serum calcium levels in the first five days.

Table-3. Comparison of serum calcium levels on the first and fifth post-operative day between the studied groups

Time	Ca level (mg/dl)		t	p
	Group I (n=50)	Group II (n=50)		
First day	8.2 ± 0.5	7.9 ± 0.8	2.249*	0.026*
Fifth day	8.1 ± 0.3	7.8 ± 0.4	0.4243*	<0.001*

Table-4 reveals that increased age is correlated with developing post-operative hypocalcemia in Group I (p<0.001) and Group II patients (p=0.004) while, gender was not related to post-thyroidectomy hypocalcemia. There was no significant difference in both groups regarding the onset of post-operative hypocalcemia as shown in Table-5 and Table-6 shows that serum calcium levels measured on the first post-operative day had a sensitivity of 58% and a specificity of 72% as a diagnostic measure for post-operative hypocalcemia.

Table-4. Comparison of the age and gender of patients with post-operative hypocalcemia and normocalcemia in the studied groups.

Demographic data	Group I				Test of significance	p	Group II				Test of significance	p
	Hypocalcemia (n=19)		Normocalcemia (n=31)				Hypocalcemia (n=31)		Normocalcemia (n=19)			
	N	%	N	%			N	%	N	%		
Gender												
Male	3	15.7	5	16.1	χ^2= 0.001	FEp= 1.000	11	35.4	7	36.8	χ^2= 0.009	0.923
Female	16	84.3	26	83.9			20	64.6	12	63.2		
Age (years)	50.8±7.6		38.7±10.1		t=4.494*	<0.001*	45.7±6.7		40.3±5.1		t= 3.014*	0.004*

Table 5: Distribution of appearance of post-operative hypocalcemia manifestations in the studied groups.

Post-operative day	Manifestations of hypocalcemia				χ^2	p
	Group I (n=19)		Group II (n=31)			
	N	%	N	%		
First day	4	26.3	9	29	0.043	0.836
Second day	8	31.5	10	32.2	0.002	0.960
Third day	7	42.2	12	38.8	0.057	0.812

Table-6. Post-operative serum calcium level as a predictor of post-operative hypocalcemia in the studied groups.

First post-operative day serum calcium	Patients with hypocalcemia (n=50)		Patients without hypocalcemia (n=50)		Sensitivity (%)	Specificity (%)
	N	%	N	%		
Normal calcium level	21	42	36	72	58	72
Low calcium level	29	58	14	28		

Table 7: Comparison of the present study with other studies

Study	Intervention		No intervention		p
	N	Hypocalcemia N (%)	N	Hypocalcemia N (%)	
Bellantone et al, (2002) [15]	26	9 (34.6%)	27	11 (24.4%)	0.78
Uruno et al, (2006) [16]	243	5 (2.1%)	304	26 (8.6%)	0.001*
Roh et al, (2009) [17]	49	18 (36.7%)	99	44 (44.4%)	0.38
The present study	50	19 (38%)	50	31 (62%)	0.047*

*: Statisticaly significant

DISCUSSION

Sousa et al, (2010)[13] reported that the incidence of post-operative hypocalcemia ranges from 1.3% to 83% and the condition may go unnoticed if not investigated carefully because it was often asymptomatic. Baldassarre et al, (2012)[14] reported that hypocalcemia incidence rates ranged widely from 0.3%–66.2% of patients after thyroid surgery. Much of the variability among results may be attributed to the numerous clinical definitions of hypocalcemia used at different institutions.

Several authors studied the value intra-operative IV calcium injection in decreasing the incidence of post-thyroidectomy hypocalcemia. Table-7 shows the results of several studies compared to the results of the present study.

Similar to the results of the present study, Uruno et al, (2006) [16]. reported significant reduction of post-operative hypocalcemia with IV injection of calcium intra-operatively, Howerver Bellantone et al, (2002)[15] and Roh et al, (2009)[17] reported no significant difference between both groups.

In the present study, it was found that hypocalcemia occurred from the immediate post-operative period up to three days after surgery. Similarly, Wu et al, (2011)[18] reported that no patient developed hypocalcemia after the third post-operative day. The critical period for serum calcium monitoring was 24-72 hours after surgery.

In another study, Chindavijak (2007)[19] reported that the symptoms of hypocalcemia may not occur in 24 hours post-operatively and may be delayed to several days. Pisaniello et al, (2005) [20] reported that hypocalcemia can occur from two to five days after surgery. Sanabria et al, (2011)[21] reported that hypocalcemia can occur from the immediate post-operative period up to five days after surgery.

It was noticed in the present study that the risk of hypocalcemia increased with age but had no relation to gender. In contrary, Prim et al, (2001)[22] showed a significant relationship between post-operative hypocalcemia and gender. This may be due to the fact that basal calcium levels tend to be lower in women, and hence develop more easily. Glinoer et al, (2000)[23] showed findings of no significant difference in hypocalcemia in relation to gender, or age.

In 2007, Chindavijak[19] studied the reliability of parathyroid gland color as a mean of assessing parathyroid gland function and concluded that the absence of discoloration was not a reliable way to determine whether the parathyroid blood supply is intact. All efforts were made to identify and carefully preserve all the parathyroid glands and its blood supply during total thyroidectomy. In the present study, the parathyroid glands were meticulously dissected from the thyroid gland, and an effort was made to identify all parathyroid glands on each side. Parathyroid glands were preserved. In two patients a parathyroid gland was accidently excised with the specimen and discovered intra-operatively and was autotransplanted in the sternomastoid muscle in those patients

Similarly, Sakorafas et al, (2005)[24] reported that autotransplantation should be strongly considered, especially when more than two parathyroid glands are identified in the specimen following thyroid resection, particularly if the operative dissection has been tedious and the vascularity of the remaining parathyroid(s) is in doubt. Pfleiderer et al, (2009)[25] on the other hand, suggested that the identification of the parathyroid glands was not a safeguard and, in fact, increased the risk of hypocalcemia probably related to either direct trauma or disruption of the blood supply due to surgical manipulation.

In the present study, early postoperative serum calcium level was used after total thyroidectomy to identify patients with a risk of developing significant hypocalcemia with a sensitivity and specificity of 58% and 72% , respectively. Similarly, Pisanu et al, (2013)[26] reported that serum calcium level showed the highest sensitivity and specificity after 24 hours (93.9 % and 100.0 %, respectively). Rosa et al, (2015)[27,32] showed that ionized calcium levels measured on the first post-operative day had a sensitivity of 45.6%, a specificity of 88.9% and an accuracy of 76.7% as a diagnostic measure for hypoparathyroidism.

Graff et al, (2010)[28] reported that postoperative serum calcium trend has been reported to be a reliable method of predicting which thyroidectomy patients will develop hypocalcemia. Jumaily et al, (2010)[29] reported that although, Parathyroid hormone (PTH) levels alone provided remarkable predictability; Intuitively, using calcium levels in conjunction with PTH levels in the first few hours after thyroidectomy might improve predictive power. They also concluded that combined calcium and PTH thresholds are better than PTH alone in their single institution studies.

Warren et al, (2002)[30] reported that the PTH assessment which has been used in parathyroid surgery for more than two decades was introduced as an early predictor of parathyroid dysfunction in thyroidectomized patients. Graff et al, (2010)[28] reported that specificity to predict hypocalcemia can be achieved by combining the early intact PTH findings with a serum calcium measurement taken 6 hours post-operatively. The combination of the two measurements represents the safest method of assessing risk and justifying the discharge of patients with favorable laboratory results on the day of surgery.

In 2001, Tredici et al[31] proposed herewith assessment of the drop in calcium levels post-operatively compared to the immediate pre-operative levels as a useful and simple predictor of hypocalcemia in patients undergoing total thyroidectomy. Adoption of 1.1 mg/dl (12% decrease of pre-operative level) can be used as cut-off for determining whether to start prophylactic calcium replacement.

The use of prophylactic calcium replacement (with or without vitamin D) after thyroidectomy seems to be gaining popularity, it is documented that giving prophylactic calcium reduces the incidence of mild to moderate symptomatic hypocalcemia.[29]

In the present study, 36% of the patients in Group I suffered from perioral numbness, tingling and positive Chvostek's sign as compared to 56% in Group II. Two percent of the patients in Group I suffered from tetany as compared to 6% in Group II. Similarly, Uruno et al, (2006)[16] reported that the prophylactic infusion of calcium solution reduced the prevalence of tetany from 8.6% to 2.1%. Uruno et al, (2006)[16] reported that symptoms of hypocalcemia, numbness, and tetany were significantly lower in patients receiving calcium gluconate injection. The serum calcium levels in the first[t] post-operative day were significantly high in the Group that received intra-operative calcium in the present study. Similarly, Uruno et al, (2006)[16]; Estari Mamidala (2014)[17] reported that serum calcium levels were significantly higher on the 1st post-operative day in patients receiving calcium gluconate injection.

CONCLUSION

Based on the data presented it may be concluded that prophylactic IV injection of calcium gluconate during total thyroidectomy is effective in lowering the risk of post-operative symptomatic hypocalcemia. Measurement of post-operative PTH serum level as well as calcium level at 6 month to detect late (chronic) hypocalcemia merit further investigations.

Conflict of Interests

Authors declare that there is no conflict of interests regarding the publication of this paper.

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