TECHNOLOGICAL ADVANCES HAVE IMPROVED SURGICAL OUTCOME IN THYROID SURGERY: MYTH OR REALITY?

H. Aydin*, S. Ferahman, S. Abdullayev, N.A. Sahbaz, A.C. Dural, D. Guzey, C. Akarsu, M. Karabulut

Istanbul Bakirkoy Dr Sadi Konuk Training and Research Hospital - General Surgery, Istanbul, Turkey

Abstract

Aim. In this study, we aimed to investigate the effects of Ultrasonic Coagulation (UC), Bipolar Energy Sealing System (BESS), Intra Operative Nerve Monitoring (IONM) and surgical experience on the complications of thyroid surgery.

Method. The data of 1627 patients who underwent thyroid surgery for various indications in our department between 2009 and 2018 were analyzed retrospectively and the effects of different technological devices on complications were investigated.

Results. Transient recurrent laryngeal nerve (RLN) palsy was higher between 2009 and 2013, when IONM was not in routine use ($p=0.029$). There were no significant differences between two energy devices (UC and BESS) in terms of transient or permanent RLN palsy, bleeding, and transient or permanent hypocalcemia. Multivariate analysis showed that young age (0.006), female gender (0.016), surgery type ($p<0.001$), and lateral neck dissection ($p=0.026$) are independent risk factors for transient hypocalcemia.

Conclusion. The results indicate that there is no superior hemostatic device. IONM and specific branching decrease transient RLN palsy. Female gender, young age, completion thyroidectomy, and lateral neck dissection were independent risk factors for the development of transient hypocalcemia.

Keywords: Bleeding, hypocalcemia, recurrent laryngeal nerve palsy, thyroidectomy complications, technological devices.

INTRODUCTION

Thyroid surgery was an extremely lethal intervention until the end of the 19th century and was even banned by the French Academy of Medicine. More recently, it has been safely applied via modern surgery with much improved complication rates. In the 20th century, contributions from T. Billroth, T. Kocher, W. Halsted, C. Mayo, G. Crile, T. Dunhill and F. Lahey

have made thyroid surgery safe and effective. Today, these seven surgeons are known as the magnificent seven of thyroid surgery (1). The procedure described and performed by the magnificent seven did not change much until the 21st century. However, the main goals of successful removal of the thyroid have not changed for years. The goals are to protect the parathyroid glands and laryngeal nerves, provide effective hemostasis, and obtain a good cosmesis (2). Today, total thyroidectomy is the gold standard in the treatment of most thyroid diseases (3).

In the last two decades, new technological devices have been developed and widely used in thyroid surgery. Endocrine surgery has become a specific division under general surgery as well. Thyroid surgeries are now performed by endocrine surgeons, and procedure-specific devices are designed for thyroid surgery such as energy-based devices for vessel sealing or probes for neuromonitorization. These are clinical standards in most high-volume centers and they reduce morbidity rates.

Considering that a postoperative bleeding can cause a life-threatening tracheal compression, the vital importance of hemostasis in thyroid surgery can be more easily understood. Although conventional knot tying is obviously a satisfactory method for the surgeon, it is undeniable that hemostatic devices are fast and practical. The bipolar energy sealing system (BESS) is a bipolar diathermy device that uses a feedback sensor system to report the completion of coagulation, and ultrasonic coagulation (UC) offers cutting and coagulation at 55 kHz based on piezoelectric crystals with mechanical vibrations (4,5).

Another important complication of thyroid surgery is recurrent laryngeal nerve (RLN) damage that can cause a wide variety of complications from voice changes to life-threatening airway obstruction from bilateral RLN injury. Although visualization of RLN is the gold standard in thyroid surgery, it is

*Correspondence to: Husnu Aydin MD, Istanbul Bakirkoy Dr Sadi Konuk Training and Research Hospital, General Surgery, Zuhuratbaba District Tevfik Saglam Street, No:11, Istanbul, 34147, Turkey, E-mail: drhusnuaydin@gmail.com

important to be certain of the functional integrity of the nerve. The basic working principle of intraoperative nerve monitoring (IONM) is to evaluate the vocal cord adductor function by using surface electrodes on the endotracheal tube; this was first used in the late 1960s (6,7). Today, IONM is used for thyroid surgery in many centers worldwide. Considering that the efficacy of these technical devices reduces complication rates in thyroid surgery, we aimed here to compare their effects on postoperative bleeding, hypocalcemia, and RLN palsy development.

MATERIAL AND METHODS

The records of patients who underwent thyroid surgery between January 2009 and November 2018 were reviewed retrospectively. We reviewed patient demographic findings, preoperative examination, surgical findings, surgeon's specialization, energy devices and IONM used during surgery, extent of surgery, morbidity, histopathology reports, and outpatient clinic follow-up notes. The patients who underwent thyroid surgery due to multinodular goiter, substernal goiter, differentiated thyroid carcinoma (DTC), toxic goiter and recurrent multinodular goiter between 18 and 80 years old were included in the study, and the exclusion criteria included patients with RLN palsy due to prior thyroid surgery. In addition, patients who were operated during the 1-month period (n=29) when the department transitioned to a specific surgical division were excluded from the study to avoid bias.

The decision of the patients to undergo central neck dissection and lateral neck dissection was made according to the ATA guidelines (8,9). Central compartment dissection was also performed in patients who underwent lateral dissection (n=68), and these procedures were added to the central compartment (n=110) analysis. The relationship between the development of hypocalcemia, RLN palsy, bleeding, and the use of BESS or UC were also analyzed. The effect of IONM on permanent and transient RLN palsy was analyzed and has been in use in our division since 2013 as a standard of care.

Vocal cord examination was performed in all patients during the preoperative period as well as in patients who developed voice changes during the postoperative period. Vocal cord paralysis that persisted for six months postoperatively was considered a permanent RLN palsy. Serum calcium and parathormone levels were followed up routinely in the outpatient clinic. Transient hypoparathyroidism was

defined as subnormal values of serum ionized calcium (reference range: 8.5-10.5 mg/dL) and PTH (reference range: 15-65pg/mL) that persisted less than six months and permanent hypoparathyroidism was defined if it lasted more than six months.

Since 2012, branching has been performed in our general surgery department; the endocrine surgery division was established with four surgeons who completed their learning curve. Our center provides specific services with a high volume (approximately 400 thyroid surgery/year). The effects of sub-specialization in general surgery on the complications of thyroid surgery were also reviewed by comparing two periods (before and after sub-specialization) of our department.

During the study period, two different hemostatic devices were used in our department: BESS (Ligasure™ Precise LF1212, Covidien, Boulder, CO, USA) and UC (Harmonic FOCUS®, Johnson and Johnson, Ethicon Endo-surgery, Cincinnati, OH, USA). The device that could be supplied according to the operating room conditions was preferred. Since 2013, intermittent IONM (Medtronic Inc., Jacksonville, USA) has also been used in all of our cases.

Ethics

This study was carried out in accordance with the 1964 Helsinki Declaration and its recent amendments. Informed consent regarding the thyroidectomy procedure and possible complications was obtained from all patients who underwent surgery. In addition, ethics committee approval was obtained from the local ethics committee (No: 2019-25-14 Date: December 23rd, 2019).

Statistical Analysis

Statistical software (JMP® version 10.0.0, SAS®, Cary, NC) was used for data analysis. Continuous variables were reported as mean ± SD or median and interquartile ranges; categorical variables were given as frequencies and percentages. The Chi-square test was used when comparing the categorical variables. Student's T-test was used to compare parametric continuous variables, and a Mann-Whitney U test was used to compare non-parametric variables. P-values of 0.05 or below were accepted as statistically significant.

RESULTS

Of the 1627 patients, 1250 (76.8%) had total thyroidectomy, 244 (14.9%) lobectomy, 97 (5.96%)

completion thyroidectomy, 36 (2.21%) near-total thyroidectomy, 42 (2.58%) central neck dissection, and 68 (4.17%) lateral neck dissection (including central compartment). While 1207 (74.19%) procedures were performed by endocrine surgery division, 420 (25.81%) were performed by general surgery department. Transient RLN palsy is higher in general surgery and without IONM group ($p=0.038$ and $p=0.029$, respectively) (Table 1). A BESS was used in 608 (37.3) patients and UC was used in 1019 (62.7%) patients. There were no significant differences between two energy devices (UC and BESS) in terms of transient or permanent RLN palsy, bleeding, and transient or permanent hypocalcemia (Table 2). Intraoperative nerve monitoring was used in 1191 (73.2%) of the patients, and a statistically significant decrease was observed in the rate of transient RLN palsy with the use of IONM ($p=0.022$) (Table 3). Comparisons of the transient and permanent causes of hypocalcemia are summarized in Table 4. Univariate and

multivariate analysis results for permanent and transient hypocalcemia showed that young age (0.006), female gender (0.016), surgery type ($p<0.001$), and lateral neck dissection ($p=0.026$) are independent risk factors for transient hypocalcemia (Tables 5 and 6).

DISCUSSION

This study overviews the changing dynamics of thyroid surgery from the perspective of complications. In this era, the energy devices used for thyroid surgery shorten the operation time and increase the comfort; IONM thus enables safer surgery. Working in sub-branches within general surgery increases the volume (both clinical and individual) and reduces the complication rate (10).

We approached the complications of thyroid surgery from two different perspectives. First, we compared the effects of two different hemostatic

Table 1. Parameters investigated as affecting factor for transient RLN palsy

Characteristics	Transient RLN Palsy (+) (n=37)	Transient RLN Palsy (-) (n=1590)	<i>p</i>
Age (mean±SD)	48.1±10.6	47.2±13.1	0.659
Gender, n (%)			
Female	31 (83.8)	1281 (80.6)	0.624
Male	6 (16.2)	309 (19.4)	
Histopathology, n (%)			
Benign	27 (73)	1208 (76)	0.673
Malignant	10 (27)	382 (24)	
Surgical Experience, n (%)			
General Surgery	15 (40.5)	405 (25.5)	0.038
Endocrine Surgery	22 (59.5)	1185 (74.5)	
Type of Surgery, n (%)			
Lobectomy	2 (5.4)	242 (15.2)	0.080
Near Total Thyroidectomy	3 (8.1)	33 (2.1)	
Total Thyroidectomy	30 (81.1)	1220 (76.7)	
Completion thyroidectomy	2 (5.4)	95 (6)	
Extent of Neck Dissection, n (%)			
Central [†]	1 (2.7)	109 (6.8)	0.733
Lateral	1 (2.7)	67 (4.2)	
The use of IONM*, n (%)			
(+)	21 (56.8)	1170 (73.6)	0.029
(-)	16 (43.2)	420 (26.4)	

RLN: Recurrent Laryngeal Nerve

* IONM: Intraoperative Nerve Monitorization

[†] As the central compartment is a component of lateral dissection, the number of lateral dissection (n=68) was included to analysis.

Table 2. Comparison of complication rates between two energy devices

Complications	UC* (n=1019)	BESS [†] (n=608)	<i>p</i>
Transient RLN Palsy, n (%)	20 (2)	17 (2.8)	0.281
Permanent RLN Palsy, n (%)	8 (0.8)	3 (0.5)	0.487
Bleeding, n (%)	10 (1)	8 (1.3)	0.532
Transient hypocalcemia, n (%)	163 (16)	93 (15.3)	0.707
Permanent hypocalcemia, n (%)	13 (1.3)	5 (0.8)	0.397

*UC: Ultrasonic Coagulation, [†]BESS: Bipolar Energy Sealing System. RLN: Recurrent Laryngeal Nerve

devices used in our clinic on complications and also examined the effects of IONM on permanent and temporary RLN palsy. Second, we examined the effects of sub-specialization in general surgery, patient factors (age and gender), pathology, and type of surgery on the development of RLN palsy and hypocalcemia.

We found no statistically significant difference between the two devices in terms of permanent and temporary RLN palsy, permanent and temporary hypocalcemia, or bleeding (Table 2). There have been many studies investigating the effects of these two devices especially on bleeding. In a meta-analysis of 23 studies and 5408 patients by Hua *et al.*, no significant

difference was found between the two devices in terms of postoperative bleeding (11). However, in the meta-analysis of Garas *et al.* (35 studies, 2586 patients), UC was found to be associated with less postoperative bleeding and postoperative hypoparathyroidism compared with BESS (12). Tirelli *et al.* showed that UC reached higher temperatures than BESS, but the two devices have no advantage over nerve damage (13).

IONM provides guidance for the surgeon to verify that the functional integrity of the RLN monitorization can be performed intermittently with the monitoring probe or continuously with a probe applied to nervus vagus (we used the intermittent monitoring).

Table 3. The effect of neuromonitorization on transient and permanent RLN palsy

Complications	The use of IONM*		<i>p</i>
	Yes (n= 1191)	No (n= 436)	
Transient RLN Palsy, n (%)	21 (1.76)	16 (3.67)	0.022
Permanent RLN Palsy, n (%)	8 (0.67)	3 (0.69)	0.971

*IONM: Intraoperative Nerve Monitorization. RLN: Recurrent Laryngeal Nerve.

Table 4. Parameters investigated as affecting factor for transient and permanent hypocalcemia

Parameters	Transient hypocalcemia		<i>p</i>	Permanent hypocalcemia		<i>p</i>
	(+) (n=256)	(-) (n=1371)		(+) (n=18)	(-) (n= 1609)	
Age (mean±SD)	45.6±11.5	47.4±13.3	0.042	43.6±12.8	47.2±13.1	0.233
Gender, n (%)						
Female	225 (87.9)	1087 (79.3)	0.001	16 (88.9)	1296 (80.5)	0.373
Male	31 (12.1)	284 (20.7)		2 (11.1)	313 (19.4)	
Histopathology, n (%)						
Benign	178 (69.5)	1057 (77.1)	0.031	11 (61.1)	1224 (76.1)	0.139
Malignant	78 (30.5)	314 (22.9)		7 (38.9)	385 (23.9)	
Surgical Experience, n (%)						
General Surgery	62 (24.2)	358 (26.1)	0.522	5 (27.8)	415 (25.8)	0.848
Endocrine Surgery	194 (75.8)	1013 (73.9)		13 (72.2)	1194 (74.2)	
Type of Surgery, n (%)						
Lobectomy	1 (0.4)	243 (17.7)	<0.001	0 (0)	244 (15.2)	0.275
Near Total Thyroidectomy	2 (0.8)	34 (2.5)		0 (0)	36 (2.2)	
Total Thyroidectomy	241 (94.1)	1009 (73.6)		17 (94.4)	1233 (76.6)	
Completion Thyroidectomy	12 (4.7)	85 (6.2)		1 (5.6)	96 (6)	
Extent of Neck Dissection, n (%)						
Central [†]	27 (24.5)	83 (75.5)	0.008	4 (3.6)	106 (96.4)	0.008
Lateral	22 (32.3)	46 (67.7)	<0.001	3 (4.4)	65 (95.6)	0.007

[†] As the central compartment is a component of lateral dissection, the number of lateral dissections (n=68) was included to analysis.

Table 5. The univariate and multivariate analysis for transient hypocalcemia

Parameter	Univariate	Multivariate
	<i>p</i>	<i>p</i>
Age	0.042	0.006
Gender	0.001	0.016
Histopathology	0.031	0.811
Surgical Experience	0.522	-
Type of Surgery	<0.001	<0.001
Central Neck Dissection	0.008	0.889
Lateral Neck Dissection	<0.001	0.026

Table 6. The univariate and multivariate analysis for permanent hypocalcemia

Parameter	Univariate	Multivariate
	<i>p</i>	<i>p</i>
Age	0.233	-
Gender	0.373	-
Histopathology	0.139	-
Surgical Experience	0.848	-
Type of Surgery	0.275	0.101
Central Neck Dissection	0.008	0.453
Lateral Neck Dissection	0.007	0.611

This is not only useful in case of recurrent or malignant disease but also allows one to safely identify RLN at the beginning of the operation and to terminate the operation by confirming the integrity of the RLN. However, IONM's benefit (continuous or intermittent) to RLN damage is controversial.

There are some meta-analyses published on this subject in the last decade. Malik and Pisanu stated that IONM did not contribute to a reduction in the rate of RLN palsy (14,15). However, Yang and Zheng found a decrease in total and transient injury in IONM cases, but the permanent injury results were not statistically significant (16,17). Bai *et al.* suggested that IONM is effective on total, temporary, and permanent RLN damage, and recommended routine use in all cases (18). Here, IONM use was found to be significantly lower in cases with transient RLN palsy, but there is no difference in terms of permanent RLN palsy ($p=0.022$) (Table 3). When cases with and without temporary RLN palsy were examined, temporary RLN palsy decreased with surgical experience and IONM use. However, there was no significant difference between the two groups in terms of age, gender, final pathology, type of operation (lobectomy, near total thyroidectomy, total thyroidectomy, or completion thyroidectomy), and neck dissection (central or lateral) (Table 1).

The routine use of IONM in our clinic started one year after the establishment of the endocrine surgery division. Four endocrine surgeons—each with sufficient experience in thyroid surgery—adapted this technology into their practice by using IONM in all their operations.

The most common complication of thyroid surgery is hypocalcemia with an incidence of 7-51%. It is not possible to predict the development of hypocalcemia during surgery, and there is no effective way to prevent it other than meticulous identification (19). In our study, we first evaluated patients who developed transient and permanent hypocalcemia in terms of age, gender, final pathology, surgical experience, type of surgery, and neck dissection (Table 4). Transient and permanent hypocalcemia were also examined with univariate and multivariate analysis (Tables 5, 6). According to our results, the only risk factor for both permanent and temporary hypocalcemia was neck dissection. In addition, female gender, young age, completion thyroidectomy, and malignancy were found to pose a risk for postoperative temporary hypocalcemia (Table 4). As a result of univariate and multivariate analyses, female gender, young age, completion thyroidectomy, and lateral neck dissection were found to be risk factors

for temporary hypocalcemia (Tables 5-6). Although female gender is stated as a risk factor for hypocalcemia in many studies, other studies have shown the opposite; there is no clear consensus on the subject of age (20-22). In our study, we found in the multivariate analysis the incidence of hypocalcemia higher in female gender and younger patients.

In our study, transient hypocalcemia is higher in lateral dissection and completion thyroidectomy groups. These two conditions were found to be independent risk factors in multivariate analysis. Since the lateral dissection group in our study included patients who underwent both central and lateral dissection, the high incidence of transient hypocalcemia in this group may be related to wide dissection and long operation times. Completion thyroidectomies are secondary interventions, and it may not always be possible to identify the parathyroid glands and maintain vascularization.

There is an inverse relationship between surgical experience and the development of hypocalcemia (23,24). The rates of this complication decreased with the experience of surgeon particularly in completion thyroidectomies and surgeries performed due to malignancy (23). Before surgical dissociation in our clinic, general surgeons who performed thyroid surgery consisted of expert surgeons who completed their learning curves in thyroid surgery and this fact may explain why there is no significant difference between the two groups in terms of complications.

Malignancy (especially advanced cancers), completion thyroidectomy, and surgeon inexperience are risk factors for permanent hypocalcemia (19). In our study, although the risk of permanent hypocalcemia was found to be higher in the neck dissection group, it was not an independent risk factor in multivariate analysis.

One of the limitations of our study is its retrospective design. Branching in our department began in 2012, but IONM was routinely used since 2013. Therefore, during the pre-branching period, IONM was not routinely used by general surgeons, and this may have caused selection bias. Other limitations of our study include the lack of postoperative bleeding measurements as the amount of drainage and bleeding complications were considered a re-operation challenge along with the absence of a 'clamp and tie' control group when evaluating energy devices.

In conclusion, we examined the effects of changes in thyroid surgery on complications over the last 10 years in our high-volume tertiary center. The

results indicate that there is no superior hemostatic device. IONM and specific branching decrease transient RLN palsy. Female gender, young age, completion thyroidectomy, and lateral neck dissection were independent risk factors for the development of transient hypocalcemia.

Conflict of interest

The authors declare that they have no conflict of interest.

References

- Hannan SA. The magnificent seven: a history of modern thyroid surgery. *Int J Surg*. 2006;4(3):187-191.
- Dionigi G, Bacuzzi A, Boni L, Rovera F, Piantanida E, Tanda ML, Diurni M, Carcano G, Luigi B, Cuffari S, Dionigi R. Influence of new technologies on thyroid surgery: state of the art. *Expert Rev Med Devices*. 2005;2(5):547-557.
- Dorairajan N, Pradeep PV. Vignette thyroid surgery: a glimpse into its history. *Int Surg*. 2013;98(1):70-75.
- Teksoz S, Bukey Y, Ozcan M, Arikan AE, Ozyegin A. Sutureless thyroidectomy with energy-based devices: Cerrahpasa experience. *Updates Surg*. 2013;65(4):301-307.
- Ecker T, Carvalho AL, Choe JH, Walosek G, Preuss KJ. Hemostasis in thyroid surgery: harmonic scalpel *versus* other techniques--a meta-analysis. *Otolaryngol Head Neck Surg*. 2010;143(1):17-25.
- Shedd DP, Durham C. Electrical identification of the recurrent laryngeal nerve. I. Response of the canine larynx to electrical stimulation of the recurrent laryngeal nerve. *Ann Surg*. 1966;163(1):47-50.
- Flisberg K, Lindholm T. Electrical stimulation of the human recurrent laryngeal nerve during thyroid operation. *Acta Otolaryngol Suppl*. 1969;263:63-67.
- Puxeddu E, Filetti S. The 2009 American Thyroid Association Guidelines for management of thyroid nodules and differentiated thyroid cancer: progress on the road from consensus- to evidence-based practice. *Thyroid*. 2009;19(11):1145-1147.
- Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, Pacini F, Randolph GW, Sawka AM, Schlumberger M, Schuff KG, Sherman SI, Sosa JA, Steward DL, Tuttle RM, Wartofsky L. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*. 2016;26(1):1-133.
- Reeve TS, Curtin A, Fingleton L, Kennedy P, Mackie W, Porter T, Simons D, Townend D, Delbridge L. Can total thyroidectomy be performed as safely by general surgeons in provincial centers as by surgeons in specialized endocrine surgical units? Making the case for surgical training. *Arch Surg*. 1994;129(8):834-836.
- Hua N, Quimby AE, Johnson-Obascki S. Comparing Hematoma Incidence between Hemostatic Devices in Total Thyroidectomy: A Systematic Review and Meta-analysis. *Otolaryngol Head Neck Surg*. 2019;161(5):770-778.
- Garas G, Okabayashi K, Ashrafian H, Shetty K, Palazzo F, Tolley N, Darzi A, Athanasiou T, Zacharakis E. Which hemostatic device in thyroid surgery? A network meta-analysis of surgical technologies. *Thyroid*. 2013;23(9):1138-1150.
- Tirelli G, Camilot D, Bonini P, Del Piero GC, Biasotto M, Quatela E. Harmonic Scalpel and Electrothermal Bipolar Vessel Sealing System in Head and Neck Surgery: A Prospective Study on Tissue Heating and Histological Damage on Nerves. *Ann Otol Rhinol Laryngol*. 2015;124(11):852-858.
- Malik R, Linos D. Intraoperative Neuromonitoring in Thyroid Surgery: A Systematic Review. *World J Surg*. 2016;40(8):2051-2058.
- Pisanu A, Porceddu G, Podda M, Cois A, Uccheddu A. Systematic review with meta-analysis of studies comparing intraoperative neuromonitoring of recurrent laryngeal nerves *versus* visualization alone during thyroidectomy. *J Surg Res*. 2014;188(1):152-161.
- Zheng S, Xu Z, Wei Y, Zeng M, He J. Effect of intraoperative neuromonitoring on recurrent laryngeal nerve palsy rates after thyroid surgery--a meta-analysis. *J Formos Med Assoc*. 2013;112(8):463-472.
- Yang S, Zhou L, Lu Z, Ma B, Ji Q, Wang Y. Systematic review with meta-analysis of intraoperative neuromonitoring during thyroidectomy. *Int J Surg*. 2017; 39:104-113.
- Bai B, Chen W. Protective Effects of Intraoperative Nerve Monitoring (IONM) for Recurrent Laryngeal Nerve Injury in Thyroidectomy: Meta-analysis. *Sci Rep*. 2018;8(1): 1-11.
- Bai B, Chen Z, Chen W. Risk factors and outcomes of incidental parathyroidectomy in thyroidectomy: A systematic review and meta-analysis. *PLoS One*. 2018;13(11).
- Coimbra C, Monteiro F, Oliveira P, Ribeiro L, de Almeida MG, Condé A. Hypoparathyroidism following thyroidectomy: Predictive factors. *Acta Otorrinolaringol Esp*. 2017;68(2):106-111.
- Kovacevic B, Ignjatovic M, Cuk V, Zivaljevic V, Paunović I. Early prediction of symptomatic hypocalcemia after total thyroidectomy. *Acta Chir Belg*. 2011;111(5):303-307.
- Edafe O, Antakia R, Laskar N, Uttley L, Balasubramanian SP. Systematic review and meta-analysis of predictors of post-thyroidectomy hypocalcaemia. *Br J Surg*. 2014;101(4):307-320.
- Paek SH, Lee YM, Min SY, Kim SW, Chung KW, Youn YK. Risk factors of hypoparathyroidism following total thyroidectomy for thyroid cancer. *World J Surg*. 2013;37(1):94-101.
- Schafer A, Shoback D. Hypocalcemia: definition, etiology, pathogenesis, diagnosis, and management. In: Rosen C, ed. *Primer on the metabolic bone diseases and disorders of mineral metabolism*. 8th ed. New York: John Wiley, 2013:573-578.