

Evaluation of voice quality in primary hyperparathyroidism patients undergoing minimally invasive parathyroid surgery

Evaluación de la calidad de la voz en pacientes con hiperparatiroides primarios sometidos a cirugía paratiroidea mínimamente invasiva

Mustafa Çalışkan¹, Taner Demirci², and Hasret Cengiz^{2*}

¹Department of Endocrinology and Metabolism, Duzce State Hospital; ²Endocrinology and Metabolism Clinic, Sakarya University Medical Faculty, Sakarya, Turkey

Abstract

Objective: Voice quality disorders remain a problem with classical surgical method which is expected to decrease with new minimally invasive methods. We aimed to examine whether there is an impairment in voice quality among our patients who have undergone open minimally invasive parathyroid surgery. **Methods:** Forty-seven primer hyperparathyroidism patients included in the study. Their video laryngoscopic evaluations and voice analyses were done in pre-operative and post-operative 6th month, and changes in the voice quality were examined. **Results:** Eighty-five (85.1%) of patients were female, with a mean age of 51.5 ± 9.4 . According to the voice analysis in the preoperative-postoperative 6th months, F0 (%): 210.616-211.443, Jitt (%): 0.699-0.735, RAP (%): 0.420-0.444, Shim (%): 2.535-2.736, NHR (dB): 0.119-0.123, and VTI: 0.044-0.045, respectively. No significant differences were observed in any of the acoustic parameters between the pre- and post-operative periods. **Conclusion:** No deterioration in voice quality was observed in patients undergoing novel minimally invasive surgical technique. In this respect we think that this new method will be much more advantageous in terms of preserving the voice quality in eligible patients.

Keywords: Primary hyperparathyroidism. Minimal invasive parathyroidectomy. Voice quality analyses.

Resumen

Objetivo: Los trastornos de la calidad de la voz siguen siendo un problema con el método quirúrgico clásico y se espera que disminuyan con los nuevos métodos mínimamente invasivos. Nuestro objetivo fue examinar si existe un deterioro en la calidad de la voz entre nuestros pacientes que se han sometido a una cirugía abierta de paratiroides mínimamente invasiva. **Métodos:** Se incluyeron en el estudio 47 pacientes con hiperparatiroidismo primario. Sus evaluaciones videolaringoscópicas y análisis de voz se realizaron en el sexto mes preoperatorio y posoperatorio, y se examinaron los cambios en la calidad de la voz. **Resultados:** Ochenta y cinco (85,1%) de los pacientes eran mujeres, con una edad media de $51,5 \pm 9,4$. Según el análisis de voz en el sexto mes preoperatorio-posoperatorio, F0 (%): 210.616-211.443, Jitt (%): 0.699-0.735, RAP (%): 0.420-0.444, Shim (%): 2.535-2.736, NHR (dB): 0,119-0,123 y VTI: 0,044-0,045 respectivamente. No se observaron diferencias significativas en ninguno de los parámetros acústicos entre el pre y postoperatorio. **Conclusión:** No se observó deterioro en

Correspondence:

*Hasret Cengiz

Adnan Menderes Caddesi,

Saglık Sokak, 195-54000

Adapazarı/Sakarya

E-mail: drhasretc@gmail.com

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la calidad de la voz en pacientes sometidos a una técnica quirúrgica mínimamente invasiva novedosa. Teniendo en cuenta que este método brindará la oportunidad de preservar la calidad de la voz en pacientes elegibles.

Palabras clave: Hiperparatiroidismo primario. Paratiroidectomía invasiva mínima. Análisis de la calidad de la voz.

Introduction

Primary hyperparathyroidism is one of the most common endocrinological diseases, affecting an average of 0.3% of the general population. Its estimated prevalence is 1-7/1000 in adults¹. Its frequency increases in the fifth and sixth decades of life and is seen 2-3 times more in women than in men. The average incidence was found 65.5 per hundred thousand for women and 24.7 per hundred thousand for men in the United States of America in 2013^{2,3}. Typically, diagnosis is made by observing hypercalcemia with high or non-suppressed normal levels of parathyroid hormone (PTH) and increased 24 h urine calcium excretion. Symptoms of osteopenia, osteoporosis, and kidney damage can be observed without hypercalcemia in patients with normocalcemic hyperparathyroidism^{4,5}.

The cause of the disease is a sporadic single adenoma, with a rate of 80-85%^{4,5}. The primary curative treatment in patients with hyperparathyroidism is surgery⁶. The classical surgical method is to detect and remove the parathyroid adenoma intraoperatively through unilateral or bilateral exploration⁷. The classical surgical method is the most effective method that has been used for years and provides a cure rate of 97-99%, especially in the hands of experienced surgeons^{8,9}. However, with the discovery of scintigraphic imaging in the 90s, pre-operative localization rates have increased dramatically. While adenoma can be imaged in 70-80% of cases by ultrasonography alone, the pre-operative adenoma localization rates exceeded 80-90% by combining ultrasonography with technetium sestamibi scintigraphy and SPECT imaging^{10,11}. Therefore, bilateral neck exploration, which is the classical surgical model, has now been replaced by less invasive and more localized methods. The minimally invasive approach continues to be used for parathyroid adenoma excision and is increasingly used in preoperatively well-localized patients and with increasing cure rates.

One of the most feared complications in neck region operations is recurrent laryngeal nerve (RLN) damage and related hoarseness. This complication, which is mostly seen after thyroid operations, is less common in parathyroid operations, which is a more localized

procedure. While the rate of temporary palsy in parathyroid operations varies between 2.5 and 6.1%, the rate of voice change due to permanent damage has been reported to be much lower (<0.5%)^{4,12,13}. The rates currently studied with minimally invasive methods seem even more satisfactory. We aimed to examine vocal changes in patients with hyperparathyroidism who underwent minimally invasive surgical approach.

Materials and methods

This study was designed prospectively. Patients with primary hyperparathyroidism admitted to our center between January 2018 and December 2019 were included in the study. After the written informed consent form was obtained from the patients, pre-operative laboratory analyses and imaging studies related to hyperparathyroidism were completed. No extra laboratory tests or radiologic procedures were performed to the patients for the study. Sound analysis tests were performed outside of the working hours in the sound analysis laboratory. Voice analysis tests were performed and recorded in the pre-operative period, and changes in voice quality, if any, were examined by repeating the same parameters in the same patients in the 6th post-operative month.

Hyper and normocalcemic primary hyperparathyroidism patients over 18 years of age were included in the study. Patients with a secondary diagnosis such as solid and hematological malignancies; granulomatous diseases that may cause hypercalcemia; chronic renal failure; severe Vitamin D insufficiency or intoxication; metabolic bone disease that may affect the parameters; and those who were pregnant were excluded from the study. Surgery was indicated in symptomatic patients according to the criteria of the Fourth International Workshop 2014 Endocrine Society Guidelines¹⁴.

Laboratory and imaging

Pre-operative imaging of the patients was done by technetium sestamibi scintigraphy and ultrasonography. Pre-operative ultrasonographies were performed by the same author with B-mode high-resolution

ultrasonography device (Logic 9 General Electric USA®). Blood samples were taken in the morning after an overnight fasting for the determination of biochemical parameters. Fasting biochemical and hormonal parameters were studied by the colorimetric method in the Abbott Architect I 2000 SR® device. Parathormone (PTH) levels were studied by the intact chemiluminescence immunoassay method, and 25-OH Vitamin D levels were studied by the radioimmunoassay method in Immulite 2000 device. Twenty-four hour urine calcium levels were recorded through atomic absorption spectrophotometry.

Operative method

Open minimally invasive parathyroidectomy technique was used as the operation technique. Under general anesthesia, curvilinear horizontal incision 2-3 cm in length was performed in focused lateral approach. Incision was performed with limited skin flap preparation according to the location of the adenoma starting from the midline to the anterior border of sternocleidomastoideus (SCM). Incision was continued throughout the platysma muscle. Anterior border of SCM was dissected and retracted laterally to expose lateral border of the strap muscles that would be retracted medially along with ansa cervicalis. Then, internal jugular vein and carotid artery were exposed and retracted laterally gently. Beneath the strap muscles, capsule of thyroid emerged and it was retracted medially to allow direct access to posterior aspect and tracheoesophageal sulcus. The parathyroid adenoma was determined and excised. Small vessels supplying parathyroid gland were electrocoagulated on the right side with bipolar cautery and then adenoma was removed. In general, RLN was located in beneath of an inferiorly located parathyroid adenoma and inferior of a superiorly located adenoma. RLN could not be defined generally due to limited incision. Finally, bleeding control was performed and the operation area was closed without draining. In the post-operative evaluation, normocalcemia was obtained in all patients. The pathological diagnosis was confirmed as parathyroid adenoma. No pathology was observed except for adenoma.

Voice analysis

The Kay/Pentax videostroboscopy for visualization of the larynx and the Computerized Speech Lab Model 4400 (CSL) for acoustic analysis of vocal quality

were used in this study. Visualization was approached by means of videostroboscopy (VLS), in which a 70 degree rigid endoscope to the Karl Storz Laryngostrobe model 8020 (Karl Storz Endoscopy Ltd., Slough, UK®) and to a 30 mm single chip color Storz endoscopic Telecam (Dx pal 202320) was passed through the oral cavity and into the posterior oropharynx so that the laryngeal cavity could be visualized. The subject was then asked to vocalize/i/as in "meet" while using their normal pitch and loudness. These stroboscopic images were used to determine true vocal fold edema, erythema, closure, mucus, and vocal fold edges. The presence or absence of vocal fold masses or lesions was reported.

The voice samples were produced in a sound-treated room at loudness levels the subjects felt comfortable with. Each subject underwent voice evaluation using the Kay/Pentax CSL (Computer Speech Laboratory) Model 4500. The CSL, a computer interfaced system, contains both hardware and software designed to analyze components of the speech signal. While the subjects were seated in a quiet office, their vocal signal was recorded directly into the system MDVP (Multi-Dimensional Voice Program). The following acoustic variables were measured: average fundamental frequency (F0), relative average perturbation (RAP), jitter, shimmer, noise-to-harmonic ratio (NHR), and voice turbulence index (VTI). The remaining variables were measured by asking the subject to sustain the vowel "a" for four seconds, using the voice quality assessment module analyze system.

Statistical analysis

Data analysis was performed using SPSS-22 for Windows (Statistical Package for the Social Sciences, SPSS Inc., Chicago IL, USA®). The variables were investigated using visual (histograms and probability plot) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk test) to determine whether or not they were normally distributed. Categorical variables were interpreted by frequency tables. We performed analyses to describe and summarize the distributions of variables. The continuous variables were expressed as mean and standard deviation or as median and interquartile range, depending on the normality of their distribution. In two different periods of the disease, paired Student's t-test was used for variables with normal distribution. The statistically significant two-tailed p-value was considered as $p < 0.05$.

Results

Forty-seven primary hyperparathyroidism patients included in the study, 85.1% of them were female and 14.9% were male. The mean age was 51.5 ± 9.4 . While adenoma could be localized in 93.6% of the patients with imaging methods, it was observed that the most common location of the tumor was the posteroinferior of the thyroid right lobe at 44.7%, and the most rare location was the superoposterior of the right lobe at 2.1%. There was a goiter simultaneously in 57.8% of all cases and the mean thyroid volume was $11.27 \pm 5.77 \text{ cm}^3$. The median volume of parathyroid adenomas was calculated as 0.51 (IQR: 0.20-0.69) cm^3 . The pre-operative baseline laboratory values were; albumin corrected total calcium; $10.88 \pm 0.55 \text{ mg/dL}$, serum phosphorus; $2.69 \pm 0.38 \text{ mg/dL}$, serum intact PTH; 158 (IQR: 120-203) pg/dL , and 25-OH-Vitamin D3; 12.90 (IQR: 7-18) ng/mL found, respectively. These and other baseline characteristics are summarized in table 1.

According to the voice analysis in the pre-operative period, F0 (%); 210.616 (± 34.342), Jitt (%); 0.699 (± 0.409), RAP (%); 0.420 (± 0.250), Shim (%); 2.535 (± 0.868), NHR (dB); 0.119 (± 0.019), and VTI; 0.044 (± 0.013) were detected. The same parameters were determined in the post-operative 6th month; F0 (%); 211.443 (± 30.870), Jitt (%); 0.735 (± 0.375), RAP (%); 0.444 (± 0.228), Shim (%); 2.736 (± 0.916), NHR (dB); 0.123 (± 0.018), and VTI; 0.045 (± 0.016), respectively. No significant difference was observed in any of the acoustic analysis parameters between pre- and post-operative periods (Table 2).

Discussion

In the present study, we examined the voice changes in our patients who underwent minimally invasive parathyroid surgery, which is a novel procedure. The main parameters in our voice analysis were fundamental frequency (Fo), relative average perturbation (RAP), jitter, shimmer, noise-to-harmonic ratio (NHR), and voice turbulence index. No significant voice quality differences or loss related to the operation were observed in post-operative voice analyses in our 47 patients.

One of the most serious complications of head-and-neck surgery is permanent loss of voice. Even when there is no recurrent nerve palsy in the post-operative period, voice complications can occur. Because of the complex pathophysiology of the formation

Table 1. Comparison of pre-operative and post-operative baseline characteristics and laboratory values

	Results* (n = 47)		
	Pre-operative	Post-operative 6 th month	p-value
Age (years)	51.5 \pm 9.4	-	
Gender (F/M)	85.1%/14.9%	-	
Tumor localization			
Not detected	6.4%	-	
Right inferior	44.7%	-	
Left inferior	40.4%	-	
Left superior	6.4%	-	
Right superior	2.1%	-	
Goiter	57.8%	-	
Thyroid volume (cm^3)	11.27 \pm 5.77	-	
Adenoma volume (cm^3)	0.51 (0.20-0.69)	-	
TSH (mIU/L)	2.09 \pm 1.31	-	
Anti-TPO positivity	25.5%	-	
Serum creatinine (mg/dL)	0.70 (0.70-0.80)	0.70 (0.70-0.80)	0.642
Pre-operative serum iPTH (pg/dL)	158 (120-203)	61.80 \pm 23.01	< 0.001
Corrected calcium (mg/dL)	10.88 \pm 0.55	9.43 \pm 0.35	< 0.001
Phosphorus (mg/dl)	2.69 \pm 0.38	3.27 \pm 0.49	< 0.001
25-hydroxyvitamin D3 (ng/ml)	12.90 (7-18)	33.52 \pm 16.73	< 0.001

TSH: thyroid-stimulating hormone.

*Continuous variables were expressed as means \pm standard deviation, or medians (interquartile ranges), depending on the normality of their distribution and categorical variables as numbers with percentages for the description of baseline characteristics.

of the voice and the involvement of many auxiliary organs in this process, apart from the vocal cords, many theoretical mechanisms are held responsible for these impairments. Potential theoretical reasons for the deterioration of voice are injury and edema of the external branch of the superior laryngeal nerve, intraoperative injuries of the external laryngeal and pre-laryngeal strap muscles (sternohyoid sternothyroid), post-operative adhesions, and laryngotracheal fixations and injuries because of orotracheal intubation¹⁵⁻¹⁷.

The prevalence of voice disorders after thyroid and parathyroid operations varies between 41% and 84% in various studies¹⁸. Voice changes lasting up to 3-6 months were seen at a rate of 11-15%¹⁹. Most of

Table 2. Acoustic analysis results in pre-operative and post-operative period

	Results*		p-value
	Pre-operative (n = 47)	Sixth month postoperatively (n = 47)	
F0 (Hz)	210.616 (\pm 34.342)	211.443 (\pm 30.870)	0.688
Jitt (%)	0.699 (\pm 0.409)	0.735 (\pm 0.375)	0.539
RAP (%)	0.420 (\pm 0.250)	0.444 (\pm 0.228)	0.511
Shim (%)	2.535 (\pm 0.868)	2.736 (\pm 0.916)	0.132
NHR (dB)	0.119 (\pm 0.019)	0.123 (\pm 0.018)	0.241
VTI	0.044 (\pm 0.013)	0.045 (\pm 0.016)	0.800

*Continuous variables were expressed as means \pm standard deviation.

Jitt: jitter; NHR: noise-to-harmonic ratio; RAP: relative average perturbation;

Shim: shimmer; VTI: voice turbulence index.

these changes are subclinical and temporary. The most common symptoms are poor or coarse voice and hoarseness. However, subjective complaints can be seen in many patients who do not experience objective voice changes in the post-operative period. Psychogenic dysphonia that develops due to diagnostic and surgical invasive procedures may also be a reason for this²⁰. Knowing the basal voice quality in the preoperative period and comparing it with the postoperative period will be useful in objectively determining which patients will benefit from early intervention and vocal physiotherapy, and will also prevent many medicolegal problems^{21,22}.

There are many studies such as our study which examine changes in voice quality after thyroid and parathyroid operations. In one of these studies among 67 patients, 21 of whom underwent parathyroidectomy, the total complication rate was found to be 0% when laryngoscopic examination combined with vocal performance questionnaire (VPQ)²³ and GRBAS²⁴ scales. Even if recurrent laryngeal nerve and superior laryngeal nerve palsy findings were detected in laryngoscopic examination, this was not reflected to the sound quality in every patient, and voice quality was better in some patients in the post-operative period²⁵. In this study, voice evaluations were made in the pre-operative period and post-operative 3rd week and month. The number of parathyroid surgery patients was limited and the follow-up time was shorter than our study. In studies conducted by Lee et al. and Henry et al., voice quality was examined among 62 thyroidectomy patients with flexible laryngoscopic examination. Quality was

evaluated objectively and subjectively with the Voice Disorder Index (VDI) (Voice Handicap Index VHI)²⁶ and Dysphonia Severity Index (DSI)²⁷. While subjective voice disorders are also seen in limited surgeries, DSI was found to be significantly different only in patients with total thyroidectomy. In addition, objective voice disorders detected in the post-operative 4th week were found to be the predictive factor for persistent voice disorders in the 6th month^{19,22}.

In a third study, shimmer and Fo parameters were examined in 46 thyroidectomy patients; the deteriorations in the shimmer were found to be more temporary than Fo. In this study, while laryngoscopic examinations were normal in 87% of patients, the maximum pitch parameter was found to be decreased¹⁷. Thomas Mushold et al. examined Fo and pitch parameters in 139 patients; 59 of whom included parathyroidectomy procedure. Pre-operative voice performance was found to be correlated with deterioration in the post-operative period; while the extend of surgery was found significant only in univariate analyses, it lost its importance in multivariate analysis¹⁸.

In another study a bit similar in terms of method to our study, perceptual auditory voice analysis, VHI²⁵, and acoustic voice analysis examinations with GRBAS scoring combined with videolaryngoscopy procedures were performed in 100 neck surgery patients and 30 breast surgery patients. In 25% of the neck surgery patients, abnormal post-operative acoustic evaluation was detected, permanent nerve damage was detected in only five of these patients, and nodule size and age were found to be significant parameters in significant voice quality change¹⁶. The surgery performed in this study is more invasive than ours. In two studies similar to this study conducted by Hong and Kim; no change was detected in phonation time and fundamental frequency (Fo), but speaking fundamental frequency and vocal range were found to be lower¹⁵. In another study, by Stojadinovic et al., the vocal jitter parameter was found to have a predicting effect on long-term vocal disorders²⁸. However, if 6 months are considered as sufficient time for detecting permanent complications, no changes were observed in our study.

All of these studies are larger studies with more patients than our series. However, these studies were generally conducted on thyroid surgery patients and the proportion of patients with parathyroidectomy is limited. Furthermore, details of parathyroidectomy procedures were not given. Probably, the procedures mentioned are the classic exploration model. In these

studies, the rate of voice complications in parathyroidectomy patients was already very low. Voice complications are expected to be very rare, as the possibility of nerve damage and other potential damage mechanisms mentioned will be less with the minimally invasive approach. Data on voice complications of parathyroid surgery are very limited. In one study, voice complications in 189 patients were shown as pre-operative 1.1% and post-operative 2.6%⁴, but minimally invasive approach parathyroidectomy patients were not evaluated due to the very low risk of this procedure.

Our study is unique in that it demonstrates the success of the minimally invasive method especially in this regard according to our knowledge. The limitations of our study are the lack of separate gender assessments in voice analysis, the absence of smoking and alcohol use data, and the absence of separate control groups that we can compare, such as classical parathyroid surgery, thyroid surgery, and non-head-and-neck surgeries. In addition, objective and subjective voice analysis and evaluation were not performed in the early post-operative period and were not compared over the long term. Our study is a single-center study with a limited number of patients. The follow-up period was only 6 months. Larger randomized controlled studies are needed to support the successful results of the minimally invasive method in terms of voice quality.

Conclusion

In our present study, we found no significant impairment in voice quality due to the operation in voice analyses in the 6th month post-operative period in our 47 primary hyperparathyroidism patients who underwent minimally invasive parathyroidectomy procedure. Parathyroid surgery is already a limited surgical procedure. It is theoretically anticipated that newly developed minimally invasive procedures cause less nerve and auxiliary vocal elements damage. Our study is the first novel study which shows objectively by voice analyses that this non-invasive method has no negative effect on voice quality to the best of our knowledge. Larger randomized controlled studies with a longer follow-up period are needed to support our data.

Conflicts of interest

The authors declare no conflicts of interest.

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of the data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients for subjects mentioned in the article. The corresponding author is in possession of this document.

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