■ Original Article

Factors increasing surgery success in primary hyperparathyroidism

Primer hiperparatiroidizm cerrahisinde başarıyı artıran faktörler

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Abstract

Aim: Standart procedure for primary hyperparathyroidism patients' is two sides neck exploration, during the last years minimal incision started to be used for primary hyperparathyroidisim patients at primary hyperparathyrodism patients. Some researchers had been done to which patients should perform minimal incision surgery that a set of indexes proposed to use. So we can try to show which parameters should be use for get better surgery results.

Material and Methods: Files of the patients, that undergo surgery for primary parathyroidism between January 2009-2016, will be studied retrospectively.

Results: There 166 patients operated for primary hyperparathyroidism. Fourteen of these patients have multiple gland disease. There is no difference for single gland disease and multigland disease patients between age and gender statistically. Multiple glands disease patients' pathology specimens lenght and weight is lower than single gland disease group statistically. Preoperative and postoperative parathormone (Pth) and calcium levels have no statistical difference. Comparing minimal invasive parathyroidectomy (MIP) and bilateral neck exploration parathyroidectomy shows there is no statistically difference between them. Avaible parameters applied advised parameters.

Conclusion: There is scoring systems, that made from combination of biochemical parameters and screening methods, seperate single gland disease and multiple gland disease. We evaluated these scoring system among our patients. CaPTHUS scoring system seems useful at our patient group. Wisconsin index is statisticaly meaningless with slight difference. So there is need to more crowded and prospective studies to be done for seperating multi gland disease and solitary adenoma. Comparing Minimal invasive parathyroidectomy and bilateral neck exploration parathyroidectomy shows that MIP is a safe procedure in selected patients.

Keywords: Primary hyperparathyroidism; single gland disease; multigland disease; minimal invasive parathyroidectomy

Öz

Amaç: Primer hiperparatiroidizm hastalarında son yıllarda standart bilateral boyun eksplorasyonu yerine, seçilmiş hastalarda minimal insizyon ile paratiroidektomi tercih edilmeye başlanmıştır. Hangi grup hastaya minimal insizyonun uygun olduğunu tespit etmek için bazı çalışmalar yapılmış ve bunlara dayanarak bir takım indeksler önerilmiştir. Biz de bu çalışmada kendi klinik olgularımızda bu parametrelerin geçerliliğini değerlendirmek amacıyla bu çalışmayı planladık.

Gereç ve Yöntemler: Çalışmamızda Ocak 2009 ve Ocak 2016 tarihleri arasında Okmeydanı Eğitim ve Araştırma Hastanesi Genel Cerrahi Kliniğinde Primer hiperparatiroidizm tanısıyla ameliyat edilmiş hastaların dosyaları retrospektif olarak incelenip sonuçlar istatistiksel olarak değerlendirildi.

Bulgular: Primer hiperparatiroidi tanısı ile ameliyat olan 166 hasta çalışmaya alındı. Bu hastaların 14'ünde çoklu bez hastalığı olduğu görüldü. Tekli bez ile çoklu bez hastaları arasında yaş ve cinsiyet açısından istatistiksel olarak fark olmadığı saptandı. Çoklu bez hastalarında piyes boyutu ve ağırlığının istatistiksel olarak daha düşük olduğu gözlendi. Ameliyat öncesi ve sonrası kalsiyum ile parathormon (Pth) değerlerinde ise bir fark olmadığı gözlendi. Minimal invazif paratiroidektomi (MIP) ya da bilateral boyun eksplorasyonu ile paratiroidektomi yapılan hastalar istatistiksel olarak karşılaştırılarak gruplar arası fark olmadığı gözlendi. Mevcut parametreler önerilen indekslere uygulandı.

Sonuç: Primer hiperparatiroidizm hastalarında tekli bez ve çoklu bez hastalığı ayrımı için biyokimyasal parametreler ile görüntüleme yöntemlerinin korelasyonuna dayalı skorlama sistemleri öneren çalışmalar mevcuttur. Bu skorlama sistemlerinin ve değerlendirme parametrelerinin etkinliği bizim hastalarımızda değerlendirildi. Bizim hastalarımızda CaPTHUS skorlama sisteminin faydalı olduğu tespit edilirken, Wisconsin indeksi ise hasta sayısının azlığından dolayı istatistiksel olarak az bir farkla anlamlandırılamamıştır. Bu yüzden tekli bez ve çoklu bez hastalığı ayrımını kolaylaştırmak için daha geniş ve prospektif çalışmaların gerekliliği söz konusudur. Minimal insizyon ile bilateral boyun eksplorasyonu karşılaştırmasında, seçilmiş hastalarda MIP için güvenilir olduğu belirlenmiştir.

Anahtar kelimeler: Primer hiperparatirodizm; tekli bez hastalığı; çoklu bez hastalığı; minimal invazif paratiroidektomi

Introduction

Primary hyperparathyroidism is most common reason of hypercalcemia for hospital applications. Primary hyperparathyroidism is a clinical condition caused by excessive parathyroid hormone (PTH) synthesis from parathyroid glands [1]. It occurs one in every 500 women and one in 2000 men after 4th decades of life. It is four fold more common in women than in men.

Standard treatment for primary hyperparathyroidism is bilateral neck exploration. First successful parathyroidectomy with bilateral neck exploration was performed in 1925 by Felix Mandl in a patient with primary hyperparathyroidism with osteitis fibrosa cystica in Vienna [2]. Devoloping new imaging techniques make it possible to perform parathyroidectomy with minimally invasive surgical techniques. Unilateral neck exploration is first performed by Jeffrey Stevens at patients with single parathyroid gland disease in 1979 [3]. Minimally invasive parathyroidectomy facilitated by intraoperative nuclear mapping was first described by James Norman and Hemant Chheda in 1997 [4].

Kebebew et al. formed CaPTHUS scoring system which could be used to differentiate between single and multiple gland disease based on blood values, ultrasonography (USG) and methoxyisobutyl isonitrile (MIBI) scintigraphy results in 2006 [5]. In 2013, Mazeh et al. demonstrated that the Wisconsin index obtained from the multiplication of PTH and calcium values could distinguish between single and multiple gland disease and thus could focus on minimally invasive surgery [6].

In our study, we aimed to determine the convenient surgical treatment in patients with primary hyperparathyroidism by detecting single or multipl gland disease cases accompanied by biochemical parameters and radiological imaging. Thus, performing focused surgery can reduce complications and the risk of re-surgery compared to the exploration of all glands.

Material and Methods

In our study, we searched retrospectively the files of the patients who underwent surgery for primary parathyroidism between January 2009 – January 2016 in Okmeydanı Training and Research Hospital Department of General Surgery.

The study was approved by The Ethic Committee of Okmeydanı Training and Research Hospital (28/6/2016–504). Informed

consent was obtained from all patients and the principles of the Helsinki Declaration were followed.

The inclusion criterias of the study were diagnosis of adenoma as histopathologically, postoperative PTH values decreased more than 50% and normal serum calcium levels of postoperatively 6 months follow-up. The exclusion criterias of the study were patients without postoperative follow-up and diagnosis of adenocarcinoma by histopathology.

Patients were evaluated with age, sex, serum calcium levels, PTH, USG and MIBI scintigraphy, tumor localization, size and weight of pathological specimen. We used Wisconsin index for evalution, Wisconsin index based on multiplication of PTH and calcium level.

We applied CaPTHUS scoring system based on PTH, serum calcium level, USG and MIBI scintigraphy. In this scoring system; serum calcium values higher than 12 mg/dl, PTH more than 2 fold higher than normal, one gland involvement in MIBI, one gland involvement in USG and the correlation between USG and MIBI findings was scored by one point. In this scoring system based on a score of 5, low sensitivity (44%), high specificity (100%) and high positive predictive value (100%) were detected in detecting single gland disease in patients who scored 3 or more.

We included 166 patients for study. 152 of them were single gland disease, and 14 patients were multiple gland disease. Statistical analysis was conducted by SPSS 15.0 and p 0.05 was accepted for statistically significant difference.

Results

One hundred sixty six patients were operated due to primary hyperparathyroidism. One hundred thirty one of these patients were female (78.9%), and 35 were male (21.1%). The mean age was 56.5 years (20-85). The mean age of the female population was 56.6 years, and the male population was 56.1 years.

The mean preoperative calcium level of the patients was 11.25 mg dl (8.3-14.9). The mean preoperative PTH value of the patients was 360.5 pg/ml (31-2479). The mean Wisconsin index that was 3606.

The mean weight of parathyroid gland was 1567 mg (110-13270 mg). The mean length of pathological specimen's longest axis was 20.8 mm (6-50).

The patients were divided into two groups, which single gland disease as "Group 1" and multiple gland disease as "Group 2". One hundred and fifty two (91.5%) patients were single gland disease, and 14 (8.5%) were multiple gland disease. 6 patients of multiple gland disease had 2 glands, and 8 patients had 4 gland hyperplasia. In Group 1, there were 124 female and 28 male patients with a mean age of 56.8 years. In Group 2, 10 female and 4 male patients with a mean age of 56.3 years. There is no statiscally significance at age and sex distrubition between two groups (Student T Test p=0.95, Mann Whitney U p=0.37).

The mean preoperative serum calcium level was 11.2 mg/dl and the mean PTH level was 326.8 pg/ml in Group 1. The mean serum calcium level of first postoperative day was 9.3 mg/dl and PTH level was 58.0 pg/ml (Table 1).

The mean preoperative serum calcium level was 11.1 mg/dl and PTH level was 188.1 pg/ml in Group 2. The mean serum calcium level of first postoperative day was 9.7 mg/dl and PTH was 38.3 pg/ml (Table 1).

Table 1: Comparison of age, preoperative serum calcium level, PTH level and weight of the groups

		Age (year)	Pre Ca (mg/dl)	Pre PTH (pg/ml)	Weight (mg)
Single Gland	N	152	152	152	152
	Mean	56.8	11.2	11.2	1686.5
(Group 1)	Standard Deviation	14.38	.87	389.8	1941.7
	Minimum	20	8.3	31.0	110
	Maximum	85	13.8	2479	13270
Multiple Gland	N	14	14	14	14
	Mean	56.3	11.1	188.1	726.4
(Group 2)	Standard Deviation	17.1	.80	147.0	556.1
	Minimum	20	9.9	47.0	240
	Maximum	84	12.7	473.4	2400

The mean weight of parathyroid gland was 1686.5 mg in Group 1 and 726.4 mg in Group 2. The mean size of the longest axis of pathological specimen was 21.2 mm in Group 1 and 15.8 mm in Group 2 (Table 2).

Table 2: Comparison of postoperative serum calcium level, PTH level, Wisconsin index and specimen size of the groups

		Post Ca (mg/dl)	Wisconsin index	Length (mm)	Post PTH (pg/dl)
Single Gland	N	152	152	152	152
	Mean	9.3	3739.3	21.2	58.0
(Grup 1)	Standard Deviation	1.0	4473.7	11.0	112.6
	Minimum	6.8	316.2	6	1.8
	Maximum	14.7	26525.3	100	1155.1
Multiple Gland	N	14	14	14	14
	Mean	9.7	2165.6	15.8	38.38
(Grup 2)	Standard Deviation	1.1	1782.8	5.8	72.3
	Minimum	8.0	512.3	10	5.1
	Maximum	12.8	5633.4	32	284.7

The mean Wisconsin index was 3739.3 in Group 1 and 2165.6 in Group 2 (Table 2). There is no statistically significance between the Wisconsin index among the groups (Mann Whitney U test p=0.06).

There is no statistically significance of preoperative serum calcium levels between groups (Mann Whitney U test p=0.51). There is no statistically significance of postoperative calcium levels between the groups (Mann Whitney U test p=0.21). There is statistically significance between the groups for preoperative PTH value (Mann Whitney U test p=0.05). There is statistically significance between the groups for postoperative PTH values (Mann Whitney U test p=0.01) (Table 3).

Table 3: Comparison of PTH level and serum calcium level of groups

	Group 1		Group 2		P value
	Mean	SD	Mean	SD	
Preop Calcium (mg/dl)	11.2	0.87	11.1	0.80	0.51
Postop Calcium (mg/dl)	9.3	1.00	9.7	1.19	0.21
Preop PTH (pg/dl)	326.8	389.86	188.1	147.05	0.05
Postop PTH (pg/dl)	58.0	112.69	38.3	72.32	0.01

The size of the specimens was found statisticaly significant in Group 1 (Mann Whitney U p=0.03). The mean weight of the specimens was found statisticaly significant in Group 1 (Mann Whitney U test p=0.002) (Table 4).

Table 4: Comparison of size and weight of specimen between groups

	Group 1		Group 2		P Value
	Mean	SD	Mean	SD	
Specimen Length (mm)	21.2	11.05	15.8	5.82	0.03
Specimen Weight (mg)	1686.5	1941.73	726.4	556.13	0.002

We used CaPTHUS for 78 of 166 patients, because of both USG and MIBI scintigraphy were only used in these 78 patients. Five of these 78 patients had multiple gland disease. CaPTHUS score of single gland disease was 0 in 5 patients, 1 in 21 patients, 2 in 15 patients, 3 in 17 patients, 4 in 12 patients and 5 in 3 patients. CaPTHUS score of multiple gland disease was 0 in 2 patients, 1 in 2 patients, 2 in 1 patient. (Figure 1).
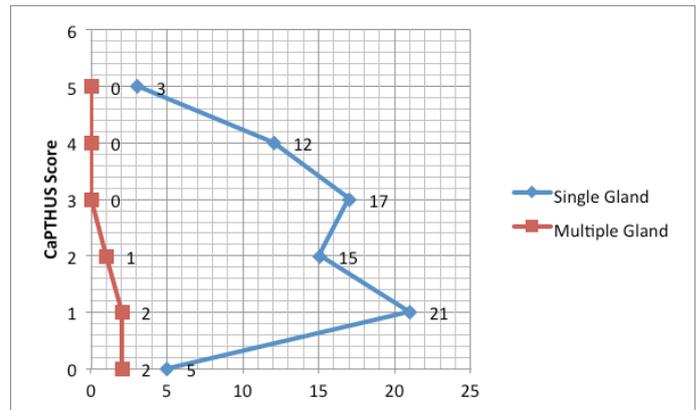

Figure 1. Distribution of the CaPTHUS Score Between Single and Multiple Gland Disease

Discussion

Primary hyperparathyroidism is a disorder caused by one or more parathyroid glands' excessive PTH synthesis [7]. Surgical treatment is essential in the treatment of primary hyperparathyroidism. The success rates of surgical treatment are 94% for the first approach and 86% for the second approach [8].

The procedure of parathyroid surgery for the treatment of parathyroid adenoma is controversial. More than %80 of primary hyperparathyroidisim is related to parathyroid adenomas. Surgical removal of the gland is preferred for treatment of adenomas [9]. Misdiagnosis of single or multiple gland disease is one of the factor that decrease the success in parathyroid adenoma surgery.

Mazeh et al.'s study on primary hyperparathyroidism, 1235 patients were examined; single gland disease was detected in 1000 patients and multiple gland disease was detected in 235 patients [6]. They formulized Wisconsin index based on multiplication of PTH and serum calcium level. Wisconsin index is significantly lower in the group of multiple gland disease (Chi Square p<0.001). We found a slightly difference with no statistical significance in Wisconsin index between the groups (p=0.06). We think this result is due to low case number.

The size of the specimen that evaluated by measuring the longest axis was found significantly lower in the multiple gland disease group. Gland weight was statistically significantly lower in the multiple gland disease group. We can use this information for determination of single gland disease by a cut-off value in the size and weight of specimen. Thus, it can show us the success of exploration while the surgery.

Kebebew et al. searched the files of 238 patients retrospectively who underwent parathyroidectomy. Single gland disease was detected in 179 patients and multiple gland disease was detected in 59 patients [5]. They developed a scoring system named CaPTHUS. Seventy eight of 166 patients in our study

had USG and also MIBI scintigraphy, and these patients were evaluated according to CaPTHUS scoring system. Five of these 78 patients had multiple gland disease. Like Kelebew et al. study none of multiple gland patients score 3 or more. Two of multiple gland disease patients score was 0, two patients scored 1 and one patient scored 2. All of these 5 patients MIBI scintigraphy and USG screening results were negative. Most experienced surgeons evaluate the patients without both of USG and MIBI scintigraphy and this is the limitation of CaPTHUS. USG and MIBI scintigraphy were found effective as imaging methods in the determination of adenoma localization and were recommended by the authors as the first screening test [10].

Parathyroid adenomas develop more frequently in lower parathyroid gland [11-13]. In our study adenomas localized upper left in 16 (%10.5) patients, upper right in 18 patients (%11,8), lower left in 68 (%44.7) patients and lower right in 50 (%32.9) patients. It was found compatible with literature [14,15].

Conclusion

The main goal of primary hyperparathyroidism surgery is to distinguish single and multiple gland disease. In this regard, scoring systems based on biochemical parameters, gland size, weight and correlation of imaging methods have been designed. CaPTHUS is one of these scoring systems and found beneficial for our study. In our study, Wisconsin index is not statistically significant due to the insufficient number of patients. During neck exploration removal of adenoma over the cut-off values can refer to adequate surgery, and it could avoid complications due to unnecessary exploration. We can prefer minimally invasive parathyroidectomy for patients which have CaPTHUS score 3 or more. Minimally invasive parathyroidectomy can reduce complications like hypoparathyroidism and vocal cord paralysis. Therefore, operating room efficiency is increased by reducing surgery time.

Declaration of conflict of interest

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References

1. Walker MD, Silverberg SJ. Primary hyperparathyrodism. Nat Rev Endocrinol 2018; 14: 115-25.

2. Cope O. The Study Of Hyperparathyroidsm At The Massachusetts General Hospital. N Engl J Med 1966; 274: 1174.

3. Stevens JC. Lateral Approach For Exploration Of The Parathyroid Gland. Surg Gynecol Obstet 1979; 148: 431.

4. Norman J, Chheda H. Minimally Invasive Parathyroidectomy Facilitated By Intraoperative Nuclear Mapping. Surgery 1997; 122: 998-1004.

5. Kebebew E, Hwang J, Reiff E, Duh QY, Clark OH. Predictors of single-gland vs multigland parathyroid disease in primary hyperparathyroidism: a simple and accurate scoring model. Arch Surg 2006; 141: 777– 82.

6. Mazeh H, Chen H, Leverson G, Sippel RS. Creation of a "Wisconsin index" nomogram to predict the likelihood of additional hyperfunctioning parathyroid glands during parathyroidectomy. Ann Surg 2013; 257: 138–41

7. John H. Yim, Gerard M. Doherty. Section 12 Operative Strategies in Primary Hiperparathyroidisim. Surgical Endocrinology, Lippincott Williams and Wilkins, Philadelphia; 2001.

8. Sheldon DG, Lee FT, Neil NJ, Ryan JA. Surgical treatment of hyperparathyroidism improves health-related quality of life. Arch Surg 2002; 137: 1022-8.

9. Palazzo F, Sadler GP. Minimally invasive parathyroidectomy, heralds a new era in the treatment of primary hyperparathyroidism. BMJ 2004; 328: 849-50.

10. Kukar M, Platz TA, Schaffner TJ et al. The use of modified fourdimensional computed tomography in patients with primary hyperparathyroidism: an argument for the abandonment of routine sestamibi single-positron emission computed tomography (SPECT). Ann Surg Oncol 2015; 22: 139–45

11. Kotan Ç, Sümer A, Öztürk ve ark. Primer hiperparatroidi: Van deneyimi, 149 Olgunun Değerlendirilmesi. Endokrinolojide Diyalog 2008; 2: 27-32.

12. Kearns AE, Thompson GB. Medical and surgical management of hyperparathyroidism. Mayo Clin Proc 2002; 77: 87-91.

13. van Dalen A, Smit CP, van Vroonhoven TJ, Burger H, de Lange EE. Minimally invasive surgery for solitary parathyroid adenoma in patients with primary hyperparathyroidism: role of US with supplemental CT. Radiology 2001; 220: 631-9.

14. Udelsman R, Pasieka JL, Sturgeon C, Young JE, Clark OH. Surgery for asymptomatic primary hyperparathyroidism: proceedings of the third international workshop. J Clin Endocrinol Metab 2009; 94: 366-72.

15. Quiros RM, Alioto J, Wilhelm SM, Ali A, Prinz RA. An algorithm to maximize use of minimally invasive parathyroidectomy. Arch Surg 2004; 139: 501-6.