GENETIC POLYMORPHISM OF CYP3A5 AS A KEY REGULATOR OF PHARMACOKINETICS OF TACROLIMUS IN KIDNEY TRANSPLANT PATIENTS: EVIDENCE IN KAZAKH POPULATION

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Abstract

Objectives: *identification of relationship of CYP3A5 genetic polymorphism with tacrolimus pharmacokinetics in kidney transplant patients in Kazakh population.*

Immunosuppressive therapy with the use of tacrolimus is one of the main ones in kidney transplantation. The survival and maintenance of satisfactory graft function in a technically perfect operation depends in most cases on immunological factors. At the same time, there is a question of a personal approach to immunosuppressive therapy of kidney recipients in patients of the Kazakh population before and after surgery. The genetic polymorphism of CYP3A5 is an important link affecting the concentration of tacrolimus and potentially able to predict the optimal dosage of tacrolimus in kidney recipients in the Kazakh population

We examined 80 kidney recipients for the presence of CYP3A5 genetic polymorphism. All the patients studied were selected from the ethnic population. Out of the total number of recipients: 37-men and 43-women. The median age was 37±8 years. All the studied patients underwent a related kidney transplant. The induction was performed using basilixamab or anti-thymocytic globulin (ATG). Immunesupressive regimen was Tacrolimus + Mycophenolic acid + corticosteroids. Postoperatively tacrolimus concentration was taken at 2, 5, 7, 10 and 14th day after the surgery.

Keywords
tacrolimus, kidney transplantation, genetic polymorphism, immunosuppression

Бүйрек трансплантациясы бар науқастардағы такролимус фармакокинетикасының негізгі реттегіші ретінде CYP3A5 генетикалық полиморфизмі: қазақ популяциясындағы деректер

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Аңдатпа

Мақсаты: *қазақ популяциясындағы бүйрек трансплантациясынан кейінгі науқастардағы CYP3A5 генетикалық полиморфизмінің такролимустың фармакокинетикасымен байланысын анықтау.*

Такролимус қолдануы иммуносупрессивті терапия бүйрек трансплантациясының негізгі әдістерінің бірі болып табылады. Техникалық тұрғыда жақсы орындалған операция кезінде трансплантаттың қанағаттанарлық функциясының сақталуы және қызмет етуі көп жағдайда иммунологиялық факторларға байланысты. Бұл ретте қазақ популяциясындағы пациенттердің бүйрек реципиенттерін иммуносупрессивті терапиясына отаға дейінгі және отадан кейінгі кезеңдерде дербес көзқарас туралы мәселе туындайды. CYP3A5 генетикалық полиморфизмі такролимус концентрациясына әсер ететін және қазақ популяциясындағы бүйрек реципиенттерінде такролимустың оңтайлы дозасын болжауға ықтимал қабілетті маңызды буын болып табылады.

Біз CYP3A5 генетикалық полиморфизмінің болуына бүйректің 80 реципиенттерін зерттедік. Зерттелген барлық науқастар этникалық популяциялардан таңдалды. Реципиенттердің жалпы санынан: 37-ерлер және 43-әйелдер. Орташа жасы 37±8 жыл болды. Барлық зерттелген науқастарға бүйрек трансплантациясы жасалды. Индукция базиликсамаб немесе анти-тимоцитарлық глобулин (АТГ) қолдану арқылы жүргізілді. Иммуносупрессивті режим такролимус + микофенол қышқылы + стероидтер болды. Отадан кейінгі кезеңде такролимус концентрациясының 2,5,7,10 және 14 күндердегі өзгерісі зерттелді.

Түйін сөздер
такролимус, бүйрек трансплантациясы, генетикалық полиморфизм, иммуносупрессия

Генетический полиморфизм CYP3A5 как ключевой регулятор фармакокинетики такролимуса у пациентов с трансплантацией почки: данные в казахской популяции

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Аннотация

Цель: выявить взаимосвязь генетического полиморфизма CYP3A5 с фармакокинетикой такролимуса у реципиентов почки в казахской популяции.

Иммуносупрессивная терапия с примененим такролимуса является одной из основных при трансплантации почки. Выживаемость и сохранение удовлетворительной функции трансплантата при технически идеально выполненной операции, зависит в большинстве случаев от иммунологических факторов. При этом встает вопрос о персональном подходе в иммуносупрессивной терапии реципиентов почки пациентов казахской популяции до - и в послеоперационном периодах. Генетический полиморфизм CYP3A5 является важным звеном, влияющим на концентрацию такролимуса и потенциально способным предсказать оптимальную дозировку такролимуса у реципиентов почки в казахской популяции

Нами было исследованно 80 реципиентов почки на наличие генетического полиморфизма CYP3A5. Все исследованные пациенты были выбраны из этнической популяции. Из общего числа реципиентов: 37 – мужчины и 43 – женщины. Средний возраст которых составил 37±8 лет. Всем исследуемым пациентам была выполнена родственная трансплантация почки. Индукция была проведена с применением базиликсамаба или анти-тимоцитарного глобулина (АТГ). Иммуносупрессиный режим был по схеме такролимус+микофеноловая кислота+стероиды. В послеоперационном периоде было исследовано изменение концентрации такролимуса на 2,5,7,10 и 14 дни.

Ключевые слова
такролимус, трансплантация почки, генетический полиморфизм, иммуносупрессия

Introduction

Kidney transplantation is the most preferable treatment option of terminal chronic kidney disease. The main advantage of kidney transplantation is that graft totally replaces the function of diseased organ. Improvement of the quality of life of patients and return to their daily activities is another great advantage of this option.

Nowadays in Kazakhstan there is an active development of kidney transplantation. One of the most important objectives is to improve the survival rates of graft. With the improvement of donor selection, surgical technique and rational immunosuppressive treatment rates of short-term graft survival greatly increased. For instance, in Kazakhstan 1-year graft survival from living related donor is 91%. Despite these high indicators of 1- year graft survival, 5-year graft survival rates remain to be low. In USA 5-year graft survival from deceased donor is up to 80%, whereas from living donor is from 82 to 90 %, respectively. So it is of paramount interest to improve the rates of long term graft survival [1].

The calcineurin inhibitor tacrolimus are the most widely used immunosuppressive agent. This drug represents a narrow therapeutic index and high inter-individual pharmacokinetic variability, so monitoring its blood level is required to avoid rejection and reduce toxicity [2].

The calcineurin inhibitors tacrolimus is catalyzed by cytochrome P450 CYP3A enzymes. CYP3A4 and CYP3A5 have been identified as the major enzymes responsible for the metabolism of calcineurin inhibitors in CYP3A subfamilies [3].

The presence of CYP3A4 and CYP3A5 in the intestinal mucosa and in hepatic cells contributes to a first-pass effect as drug molecules are metabolized prior to reaching the systemic circulation. Genetic polymorphism in these 2 enzymes accounts for a significant part of the interindividual variability observed with tacrolimus bioavailability. The best studied genetic variation is in the CYP3A5 gene [4].

The wild-type CYP3A5 *1 allele is associated with greater production of functional CYP3A5 enzyme, thus leading to higher drug-metabolizing activity by CYP3A overall. The CYP3A45*1/*1 genotype increases tacrolimus clearance by 2-fold, while the heterozygous CYP3A5*1/*3 genotype results in approximately 1.7-fold greater clearance compared to the CYP3A5*3/*3 population [5-7] CYP3A5 *3/*3 has 48% lower oral clearance compared to CYP3A5 expressers [8].

In this way, we investigated the personalization and rationalization of immunosuppressive treatment. In our country as in whole world genetic factors, determining long-term kidney graft survival, represents a great relevancy in transplantation. The determination of genetic polymorphism of CYP3A5 gives us the opportunity to predetermine the changes in blood concentrations of tacrolimus, better control of immunosuppressive therapy and this will positively affect the long-term graft survival.

The study aimed to determine the significance of CYP3A5 genetic polymorphism in regulation of

tacrolimus pharmacokinetics in kidney transplant patients in Kazakh population.

Material and Methods

We retrospectively studied 80 kidney transplant recipients. Of them – 32 were female and 48 male patients. Mean age 36±12 years old. All patients were selected from Kazakh population and were investigated for CYP3A5 genetic polymorphism (single-nucleotide polymorphism, rs776746, also known as 6986A>G). Patients underwent related living donor kidney transplantation. There were no substantial differences in surgical technique or warm/cold ischemic times. Graft function was immediate in all cases.

Immunosuppression

Induction therapy was either with basiliximab or Anti-Tymocit globulin. Immunosuppressive regimen was Tacrolimus + Mycophenolic acid + corticosteroids.

Tacrolimus concentration was measured by chemiluminescence method. Tacrolimus was administered 0.1 mg/kg/ body weight. Tacrolimus concentration level was taken initially at 2 postoperative days and furtherly at 5th, 7th, 10th and 14th, respectively. Dose addition/reduction was by 1.0 mg. Accepted tacrolimus target level was 10-13 ng/ml.

Statistics

Patients were arranged according to the results by Fisher's test and correlation of graft function and genetic polymorphism of CYP3A5 was assessed Mann-Whitney U test. $P < 0.05$ was given as significant.

Results

According to the results in our study 61.25% (n=49) of patients were homozygotes, CYP3A5*3*3 carriers (non-expressers) and 38.75% (n=31) were heterozygotes, CYP3A5*1*3 carriers (with one expressor allele). Patients were arranged by sex/type of polymorphism by Fisher's test. There were no significant differences in sex/CYP3A5 genetic polymorphism in patients Table 1.

Patients were divided into 2 groups: homozygotes and heterozygotes. Tacrolimus concentration was measured on 2, 5th , 7th , 10th and 14th days after surgery and at discharge. There were significant differences in concentrations on 2nd, 5th, 7th and 10th days in both groups ($p = 0.02$, 0.01, 0.12 and 0.016, respectively). There were no significant statistical differences in tacrolimus concentration on 14 day after the surgery and at discharge ($p = 0.085$ and 0.171, respectively). In both groups tacrolimus almost reached target level at the end of 2nd week, but in heterozygotes increase was more gradual and predictable rather than in homozygotes (Fig.1). There were no substantial differences in graft function (Table 2). Creatinine level normalized gradually in both groups and there was not significant differences in both groups at discharge ($p = 0.834$ (Fig.2)

Discussion

Tacrolimus is a commonly used immunosuppressant after kidney transplantation. It has a narrow therapeutic range and demonstrates wide interindividual variability in pharmacokinetics, leading to potential underimmunosuppression or toxicity. Genetic polymorphism in CYP3A5 enzyme expression contributes to differences in tacrolimus bioavailability between individuals. Individuals carrying one or more copies of the wild-type allele *1 express CYP3A5, which increases tacrolimus clearance. CYP3A5 expressers require 1.5 to 2-fold higher tacrolimus doses compared to usual dosing to achieve therapeutic blood concentrations. Individuals with homozygous *3/*3 genotype are CYP3A5 nonexpressers. CYP3A5 nonexpression is the most frequent phenotype in most ethnic populations,

			CYP3A5*1*3	CYP3A5*3*3	p
Sex	Female	N	13	19	1,000
		%	42,0%	38,7%	
	Male	N	18	30	
		%	58,0%	61,2%	
Total %		N	31	49	
		100,0%	100,0%		

Table 1.
Arrangement of patients due to gender-CYP genetic polymorphism relationship

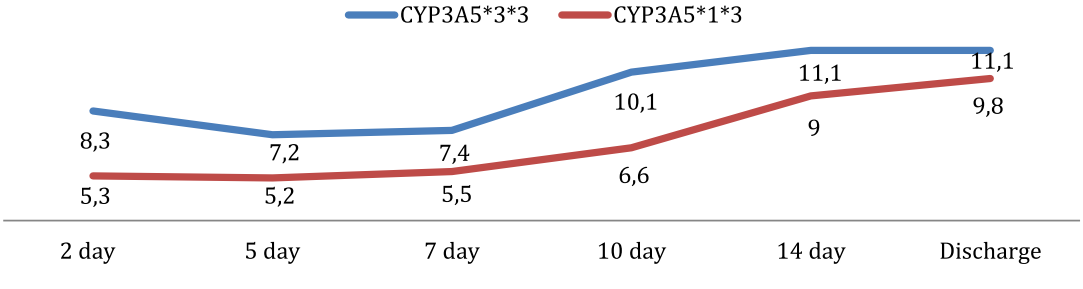

Fig. 1
Changes of tacrolimus concentration (ng/ml) with CYP 3A5 genetic polymorphism

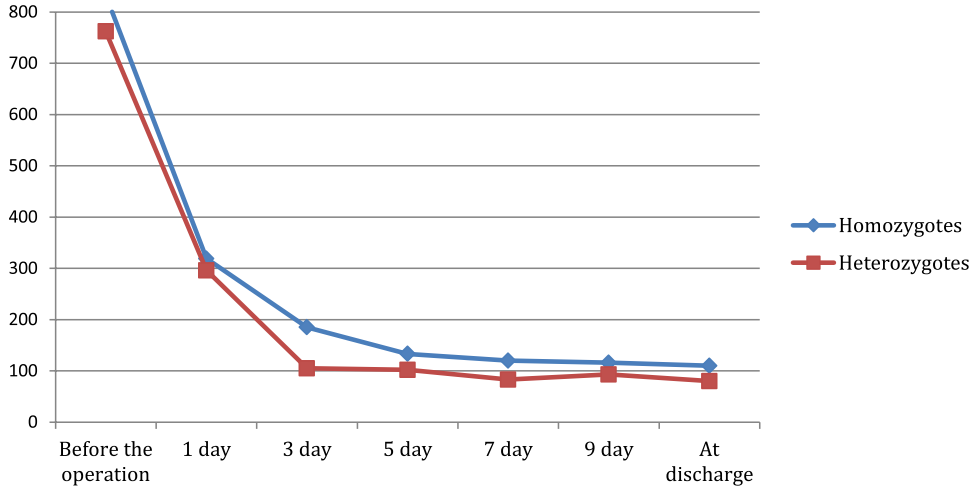

Fig. 2
Changes of creatinine (μmol/l) level in kidney patients with CYP3A5 genetic polymorphism
Notes:
B - Time before the operation, and D - time at discharge

Table 2.
Changes of Tacrolimus concentration in both groups (Mann - Whitney U test)

Type of poymorphism		2 day	5 day	7 day	10 day	14 day	Discharge
CYP3A5*1*3	N	31	31	31	31	31	31
	Average	5,3	5,2	5,5	6,6	9,0	9,8
	Std. Deviation	3,0	2,6	1,7	2,2	2,6	1,9
	Median	4,4	4,6	5,5	6,8	8,3	9,3
	Range	10,2	9,8	6,00	7,90	8,9	5,0
CYP3A5*3*3	N	49	49	49	49	49	49
	Average	8,3	7,2	7,4	10,1	11,1	11,1
	St. D	5,2	2,4	2,2	3,9	4,4	2,9
	Median	7,1	6,5	6,8	10,0	9,9	11,0
	Range	27,0	8,2	8,20	14,10	19,4	13,7
p		0,020	0,010	0,012	0,016	0,085	0,171

except blacks. Differences between CYP3A5 genotypes in tacrolimus disposition have not translated into differences in clinical outcomes, such as acute rejection and graft survival. Therefore, although genotype-based dosing may improve achievement of therapeutic drug concentrations with empiric dosing, its role in clinical practice is unclear [11].

The effect of CYP3A5 *1 and *3 alleles on tacrolimus pharmacokinetics is consistently and extensively documented across a multitude of studies over the past 15 years [9, 10]. The goal of genotype-based dosing is to provide empiric dosing that allows rapid achievement of therapeutic drug concentrations, particularly in the initial days after transplant. In one retrospective study, an empiric weight-based starting dose of 0.1 mg/kg was used to target a therapeutic range of 4-8 mcg/mL [12]. Among CYP3A5 non-expressers (CYP3A5*3/*3), 50% of patients achieved the target range by day 3 of therapy. Among CYP3A5 expressers (CYP3A5*1/*3 or *1/*1), however, only 35.3% of patients achieved through concentrations within the therapeutic range by day 3. Use of therapeutic drug monitoring did allow for rapid dosing correction. By day 7, 64.2% of expressers, compared to 55.4% of non-expressers, achieved therapeutic trough concentrations. These results suggest that CYP3A5 genotyping is likely more useful if available before kidney transplant.

Similar results were received in clinical trial conducted by Quteineh L. and co-authors. In total 136 kidney recipients were studied. As was in previous investigation patients with CYP3A5*1*1 genotype need higher doses of tacrolimus to reach the target concentration. Interestingly the situation remained the same for subsequent 6 and 12 months. CYP3A5 genetic polymorphism was not associated with tacrolimus nephrotoxicity but influenced the dose adjustment. Authors suggest preoperative evaluation of CYP3A5 genetic polymorphism, especially CYP3A5*1 carriers [13].

In kidney recipients with CYP3A5*1*1 and *1*3, tacrolimus concentration remained low even after dose adjustment in contrast to CYP3A5*3*3 carriers. For instance, half of patients with CYP3A5*1 after 7 days from initiation of immunosuppression tacrolimus was less than 5 ng/ml, whereas in CYP3A5*3 carriers – more than 20 ng/ml. Thus this genetic factor is one of most important regulators of rational immunosuppressive treatment [14].

Acute rejection episodes were more frequent in expressers, and they may require higher doses of tacrolimus. Similarly, tacrolimus nephrotoxicity was more frequent in non-expressers. Therefore, CYP3A5 polymorphism analysis before renal transplant may help determine the optimal dose of tacrolimus in this population and prevent acute rejection episodes or tacrolimus toxicity [9, 15].

In our clinical study there were not CYP3A5*1*1 carriers, thus in Kazakh population there are seen only *1*3 and *3*3 genetic polymorphisms. In all cases graft function was immediate. There were not any cases of acute graft rejection in both groups. There was a statistical difference in tacrolimus pharmacokinetics in both groups, but this does not affect graft function and all patients were discharged with good functioning graft. There was also a correlation of tacrolimus concentration with body mass. So in patients with high body mass index tacrolimus had peak rises up to 20 ng/ml soon after the surgery and subsequently gradual decline. In this patients creatinine level normalized slowly. Tacrolimus didn't have any correlation with age and sex.

Conclusion

It is obvious from received results, that genetic polymorphism of CYP3A5 influences tacrolimus blood concentrations, that appear to be key factor in immunesupression [16]. Even in rational choice of dose of immunosuppressive agent, genetic factor must be considered as well. In order to improve long-term graft survival rates it is important to maintain therapeutic concentration of tacrolimus in blood. In this way it is important to determine the CYP3A5 genetic polymorphism preoperatively [17], as one of approved genetic determinants of graft survival and for the correct selection of initial dose.

In Kazakh population most patients are non-expressers and this is a national characteristic. Patients reached tacrolimus trough level quickly at low doses. We expect that genotype-based dosing may be the key factor in determination of preferred doses of tacrolimus in each individual. Moreover, genotype-based patterns of dose regimen are now being investigated in order to ease the choice of suitable dose regimen. Rational immunosuppressive treatment leads to prolonged graft function and genetic factors appear to be the key factor in drug dose selection.

References

1. Barry A, Levine M. (2010) A systematic review of the effect of CYP3A5 genotype on the apparent oral clearance of tacrolimus in renal transplant recipients. Ther Drug Monit. 32(6): 708-714.
2. Boughton O, Borgulya G, Cecconi M, Fredericks S, Moreton-Clack M, MacPhee IA. (2013) A published pharmacogenetic algorithm was poorly predictive of tacrolimus clearance in an independent cohort of renal transplant recipients. Br J Clin Pharmacol. 76(3): 425-431.
3. Chen P, Li J, Li J, Deng R, Fu Q, Chen J, Huang M, Chen X, Wang C. (2017) Dynamic effects of CYP3A5 polymorphism on dose requirement and trough concentration of tacrolimus in renal transplant recipients. J Clin Pharm Ther. 42(1): 93-97.
4. Cheng Y, Li H, Meng Y, Liu H, Yang L., et al. (2015) Effect of CYP3A5 polymorphism on the pharmacokinetics of tacrolimus and acute rejection in renal transplant recipients: experience at a single centre. Int J Clin Pract Suppl. 183: 16-22.
5. Glowacki F, Lionet A, Buob D, Labalette M, Allorge D., et al. (2011) CYP3A5 and ABCB1 polymorphisms in donor and recipient: impact on Tacrolimus dose requirements and clinical outcome after renal transplantation. Nephrol Dial Transplant. 26(9): 3046-3050.
6. Jacobson PA, Oetting WS, Brearley AM, Leduc R, Guan W., et al. DeKAF Investigators. (2011) Novel polymorphisms associated with tacrolimus trough concentrations: results from a multicenter kidney transplant consortium. Transplantation. 91(3): 300-308.
7. Lypez-Montenegro Soria MA, Kanter Berga J, Beltrбn Catalбn S, Milara Payб J, Pallardy Mateu LM, Jimйnez Torres NV (2010) Genetic polymorphisms and individualized tacrolimus dosing. Transplant Proc. 42(8): 3031-3033.
8. MacPhee IA, Fredericks S, Tai T, Syrris P, Carter ND, Johnston A, Goldberg L, Holt DW. (2004) The influence of pharmacogenetics on the time to achieve target tacrolimus concentrations after kidney transplantation. Am J Transplant. 4(6): 914-919. (in Eng)
9. Nair SS, Sarasamma S, Gracious N, George J, Anish TS, Radhakrishnan R. (2015) Polymorphism of the CYP3A5 gene and its effect on tacrolimus blood, Exp Clin Transplant. 13(1): 197-200.
10. Oetting WS, Schladt DP, Guan W, Miller MB, Remmel RP., et al. DeKAF Investigators. (2016) Genomewide Association Study of Tacrolimus Concentrations in African American Kidney Transplant Recipients Identifies Multiple CYP3A5 Alleles. Am J Transplant. 16(2): 574-582.
11. Lucy Chen and G. V. Ramesh Prasad (2018) CYP3A5 polymorphisms in renal transplant recipients: influence on tacrolimus treatment Pharmgenomics Pers Med. 11: 23–33.
12. Quteineh L, Verstuyft C, Furlan V, Durrbach A, Letierce A., et al. (2008) Influence of CYP3A5Genetic Polymorphism on Tacrolimus Daily Dose Requirements and Acute Rejection in Renal Graft Recipients. Basic & Clinical Pharmacology & Toxicology. 103(6): 546–552.
13. Rojas L, Neumann I, Herrero MJ, Bosy V, Reig J., et al. (2015); Effect of CYP3A5*3 on kidney transplant recipients treated with tacrolimus: a systematic review and meta-analysis of observational studies. Pharmacogenomics J. 15(1): 38-48.
14. Sakaeda T, Nakamura T, Okumura K. (2003) Pharmacogenetics of MDR1 and its impact on the pharmacokinetics and pharmacodynamics of drugs. Pharmacogenomics. 4(4): 397-410.
15. Shi Y, Li Y, Tang J, Zhang J, Zou Y, Cai B, Wang L. (2013) Influence of CYP3A4, CYP3A5 and MDR-1 polymorphisms on tacrolimus pharmacokinetics and early renal dysfunction in liver transplant recipients. Gene. 512(2): 226-231.
16. Terrazzino S, Quaglia M, Stratta P, Canonico PL, Genazzani AA. (2012) The effect of CYP3A5 6986A> G and ABCB1 3435C>T on tacrolimus dose-adjusted trough levels and acute rejection rates in renal transplant patients: a systematic review and meta-analysis. Pharmacogenet Genomics. 22(8): 642-645.
17. Zhang X, Liu ZH, Zheng JM, Chen ZH, Tang Z, Chen JS, Li LS. (2005) Influence of CYP3A5 and MDR1 polymorphisms on tacrolimus concentration in the early stage after renal transplantation. Clin Transplant. 19(6): 638-643.

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MODERN PRINCIPLES OF SURGERY TREATMENT OF PATIENTS WITH NODULAR GOITER

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Abstract

Purpose of the study. *To justify and confirm the differentiated approach to choosing the volume of surgical intervention in benign nodular goiter.* ***Materials and methods.*** *A prospective analysis of 180 patients who underwent thyroid surgery was performed; 11 (6.1%) were men and 169 (93.9%) were women aged 20-65 years. The duration of the patients' disease was 8 months to 12 years. All patients with benign non-toxic goiter underwent a thorough evaluation of changes in the level of thyroid hormones in serum, ultrasound of the thyroid gland, and aspiration biopsy of the thyroid gland.* ***Results.*** *In laboratory studies, a high level of malignancy is observed in patients with higher levels of TSH and antibodies, TG and antibodies, TPO. There were no significant differences in the values of T3 and T4. In the ultrasound study, the average and maximum diameter of malignant nodes were significantly smaller than that of benign ones (1.99 ± 1.88 cm; p < 0.001). The difference between surgical procedures described as subtotal, total, and hemi-thyroidectomy was statistically significant. In 128 (71.1%) patients nodes were located in one lobe, 68 (37.8%) patients had multiple nodes, and 52 (28.9%) had solitary nodes in one of the thyroid lobes. In-traoperatively, 68 (37.7%) patients underwent cytomorphological examination of removed thyroid tissue. Hemithyroidectomy was performed in only 57 (31.6%) patients. Subtotal thyroidectomy was performed in 78 (43.3%) patients, and total thyroidectomy was performed in 45 (25%) pa-tients. With the development of hematoma, one patient was re-operated after total thyroidectomy. Hypoparathyroidism was diagnosed in 2 (4.4%) patients after thyroidectomy, and in 1 (1.3%) patient after subtotal thyroidectomy. 3 patients had transient laryngeal paresis after thyroidectomy. Hypothyroidism developed in 14 (24.6%) patients after hemithyroidectomy, in 50 (64.1%) patients after subtotal thyroidectomy and in 45 (100%) after thyroidectomy.* ***Conclusion.*** *The decision of surgical intervention should be differentiated with respect to the choice of surgical intervention tactics.*

Keywords
thyroidectomy, subtotal thyroidectomy, hemithyroidectomy, hypothyroidism, hypoparathyroidism

Түйінді зобпен аурытын науқастарды хирургиялық емдеудің заманауи принциптері

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Аңдатпа

Зерттеу мақсаты. *Қатерсіз түйінді жемсау кезіндегі отаның көлемін анықтауды таңдаудағы дифференциалды тәсілдемені негіздеу және бекіту.* ***Материалдар мен әдістер.*** *Қалқанша безіне ота жасатқан 180 науқасқа проспективті талдау жүргізілді. Оның ішінде – 20-65 жас аралығындағы 11 (6,1%) ер адамдар және 169 (93,9%) әйелдер. Науқастардың ауру ұзақтығы – 8 айдан 12 жылға дейін. Қатерсіз токсикалық емес жемсауы бар науқастарлың барлығы қан сарысуындағы ҚБ гормондары деңгейінің өзгерістерін мұқият бағалаудан, қалқанша безінің УДЗ-сынан, қалқанша безінің аспирациялық биопсиясынан өтті.* ***Нәтижелер:*** *Зертханалық зерттеу кезінде қатерліліктің жоғары деңгейі ТТГ және АТ, ТГ және АТ, ТПО жоғары деңгейі бар науқастарда байқалды. Т3 және Т4 мәндерінде нақты айырмашылық анықталған жоқ. УДЗ зерттеу кезінде қатерсіз түйіндерге қарағанда, қатерлі түйіндердің орташа және макси-малды диаметрі едәуір аз болды (1,99±1,88 см; p<0,001). Субтоталды, тоталды және гемитиреоидэктомия ретінде сипатталған хирургиялық шаралар арасындағы айырмашылық статистикалық маңызды болды. Науқастардың 128-інде (71,1%) түйіндер бір бөлікте, науқастардың 68-інде (37,8%) көптеген түйіндер болған, ал 52 (28,9%) науқаста қалқанша безінің бір бөлігінде жеке түйіндер болды. Интраоперациялық кезеңде 68 (37,7%) науқастың қалқанша бездерінің жойылған тіндеріне цитоморфологиялық зерттеу жүргізілді. 57 (31,6%) науқасқа гемитиреоидэктомия жасалды. 78 (43,3%) науқасқа субтоталды тиреоидэктомия, ал 45 (25%) науқасқа тоталды тиреоидэктомия орындалды. Гематоманың дамуына байланысты тоталды тиреоидэктомиядан кейін бір науқасқа, гипопаратиреоз тиреоидэктомиядан кейін 2 (4,4%) науқасқа, субтоталды тиреоидэктомиядан кейін 1 (1,3%) науқасқа қайтадан операция жасалды. 3 науқаста тиреоидэктомиядан кейін көмейдің транзиторлық жарасы пайда болды. Гемитиреоидэктомиядан кейін 14 (24,6%), субтоталды тиреоидэктомиядан кейін 50 (64,1%) және тиреоидэктомиядан кейін 45 (100%) науқаста гипотиреоз дамыды.* ***Қорытынды.*** *Оталық араласудың шешімі отаның тактикасын таңдауға қатысты сарапануы тиіс.*

Түйін сөздер
тиреоидэктомия, субтоталды тиреоидэктомия, гемитиреоидэктомия, гипотериоз, гипопаратиреоз