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A B S T R A C T

of the dissertation for the degree of Doctor of Philosophy

**COMPLEX EVALUATION OF THE RESULTS OF TREATMENT OF
CRYPTORCHIDISM IN CHILDREN**

Speciality: 3230.01 - Pediatric Surgery

Field of science: Medicine

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GENERAL CHARACTERISTICS OF THE STUDY

Actuality of problem: Cryptorchidism remains one of the most actual and medical-social problems of modern medicine. The incidence of cryptorchidism in premature infants varies from 1-3% and in premature infants more than 30%.¹ Although various aspects of this pathology have been studied for many years, many issues regarding the etiology, pathogenesis, treatment, and rehabilitation of patients remain unclear. Despite the improvement of traditional surgeries used in the treatment of cryptorchidism, postoperative retraction of the testes is about 13 %.²

According to modern ideas, mesenchymal tissue plays a key role in the process of hormonal regulation and migration of the testicle during intrauterine development. The source of the interstitial tissue of the testicle is the mesenchymal tissue consisting of fibroblasts, from which Leydig cells are then differentiated from these fibroblasts. It is the active synthesis of dehydro-epiandrosterone and testosterone by Leydig cells that regulates the descent of the testes from the peritoneal area to the scrotum.³

Tissue biopsies have been used for many years to diagnose connective tissue (CT) dysplasia. Although this method has diagnostic importance, it makes it difficult to assess the dynamic evaluation of tissue dysplasia during cryptorchidism and to study the results after correction. So, to do repeatedly biopsies are invasive and lose their relevance in daily practice.

¹Suresh, N.M. Evaluation of incidence of cryptorchidism with special reference to anatomical and clinical aspects / N.M. Suresh, K. Subramanya, B. Apurva [et al.] // International Journal of Contemporary Pediatrics, -2018. vol.5. – p. 1388-1392.

²Ahmed, A. Y. Unsatisfactory testicular position after inguinal orchidopexy: Is there a role for upfront laparoscopy? / A.Y. Ahmed, M.M. Mahmoud, H.A. Mohamed [et al.] // Arab Journal of Urology, - 2020. vol.18. – p. 48-53.

³Foresta, C. Role of hormones, genes and environment in human cryptorchidism // C. Foresta, D. Zuccarello, A. Garolla [et al.] // Endocrine Reviews, - 2008. vol. 29. - p. 560-580

Therefore, to detect connective tissue dysplasia or disorder has recently been widely used the determination of CT metabolites-glycosaminoglycan (GAG) and oxyproline (OP), in body fluids.

Thus, the disruption of the synthesis and breakdown of collagen proteins during connective tissue dysplasia is characterized by changes in the secretion of OP and GAG in the body's biological fluids.⁴ The idea of determining and correction the level of connective tissue metabolites in the urine and blood during undescended testis opens a new direction in terms of improving the results of treatment of cryptorchidism.

In recent years, the development of surgery has also opened up new directions in the surgical treatment of cryptorchidism. One candidate's work on improving the treatment of cryptorchidism has been carried out in our republic.⁵ This dissertation mainly studies the hormonal status of patients with cryptorchidism, the application of Sokolov-Kitli surgery in a new modification and the consequences of this operation.

All of the above indicate that the role and correction of connective tissue dysplasia in children during cryptorchidism and postoperative recurrence have not been adequately studied. At the same time, no specific guidelines have been developed for the selection of inguinal and scrotal incisions for orchiopexy during cryptorchidism and testicular ectopia, and the cause of postoperative retraction has not been comprehensively assessed.

⁴Кадурина, Т. И., Аббакумова, Л.Н. Оценка степени тяжести недифференцированной дисплазии соединительной ткани у детей // Медицинский вестник Северного Кавказа, - 2008. Т. 2, № 10, - с. 15-21.

⁵Ismayilov, M.U. Near and far results of surgical treatment of cryptorchidism in children / Author's abstract of the doctoral dissertation on pediatric surgery / - Baku, - 2007. - 26 p.

The aim of study: Detect the role of connective tissue dysplasia and organize strategy of treatment during cryptorchidism.

Research objectives:

1. To determine the role of connective tissue dysplasia in inguinal and recurrent cryptorchidism in children.
2. To assess the hormonal status and ultrasonographic size of the testicle in children with inguinal and recurrent cryptorchidism.
3. Light and electron microscopic examination of the gubernaculum during inguinal cryptorchidism.
4. To study the role of connective tissue dysplasia and hormonal status in inguinal and recurrent cryptorchidism and to develop medical correction.
5. Choice of surgical tactics in open orchiopexy operations depending on the location of the testis

Scientific novelty of the research.

- Blood and urine levels of CT metabolites were studied to investigate the role of CT dysplasia in cryptorchidism and relapsed cryptorchidism
- Light and electron microscopic studies were performed on biopats taken from the gubernaculum during cryptorchidism
- An examination and treatment program based on a comprehensive assessment of connective tissue dysplasia and hormonal status in children with cryptorchidism will reduce the number of unsuccessful outcomes, regardless of the form of cryptorchidism.

The main provisions of abstract.

- There is an increase level of CT metabolites in the blood and urine during cryptorchidism and recurrent cryptorchidism
- Light and electron microscopic examination of biopats taken from the gubernaculum during cryptorchidism revealed the formation of degenerative changes in collagen fibers, as well as an increase in the amount of GAGs, which are part of proteoglycans.

- It is noted that the size of the testicle, which underwent a pathological process during cryptorchidism, is small compared to a normal testicle. During relapsing cryptorchidism, this difference becomes even more pronounced.

- Significant changes in hormonal parameters, especially testosterone levels. Although LH and FSH were low compared to the control group, they met the literature standards.

Practical significance of the research:

- The role of connective tissue dysplasia in children during cryptorchidism and the formation of secondary retractions will be determined and drug correction will be developed and applied.

- The type of surgical treatment will be optimized for inguinal undescended testis

Application of the results of scientific work. The results of scientific research are applied in the Department of Pediatric Surgery of the Educational-Surgical Clinic by Medical University of the Ministry of Health of the Republic of Azerbaijan. The obtained results are used in the teaching program of the Department of Pediatric Surgery of the Azerbaijan Medical University.

Relationship of the research with the plan of medical sciences: The dissertation is a fragment of the research work on "Diagnosis and treatment of congenital malformations of the abdominal organs and anterior abdominal wall in children", state registration is: 108

Approbation of the dissertation. The materials of the dissertation were discussed at the Scientific-Practical Conference 2015 Actual Problems of Medicine, dedicated to the 92nd anniversary of national leader Heydar Aliyev, at the Scientific-Practical Congress on Pediatric Surgery (2019) dedicated to the 80th anniversary of the Azerbaijan Medical University.

Preliminary interdepartmental discussion of the dissertation was held on January 15, 2020 (Protocol №1) in Azerbaijan Medical University with the participation of Pediatric Surgery, Urology, I

Surgical Diseases, II Surgical Diseases, III Surgical Diseases, Traumatology and Orthopedics, Resuscitation and Intensive Therapy departments and TSC staff.

The scientific seminar discussion of the dissertation was held on April 28, 2021 (Protocol №2).

Published scientific works. 8 scientific articles and 6 theses on the topic of the dissertation were published.

Volume and structure of the dissertation. The dissertation consists of 165 pages, introductory part, 4 chapters, conclusions, practical recommendations and bibliography. The dissertation is illustrated with 14 pictures, 26 graphic and 14 tables. The bibliography covers 201 sources. 12 of them are works of Azerbaijani, 19 Russian and 170 other foreign scientists.

The content of abstract

To detect changes in CT during cryptorchidism, CT metabolites, as GAGs, total and free OP were analyzed in body fluids (urine, blood), and electron microscopic and histological examinations were performed on biopsies taken from the gubernaculum during orchiopexy surgery. These metabolites can be used to obtain information about connective tissue. Thus, an increase in the level of these metabolites in the blood indicates a pathological process in which CT occurs. On the other hand, histological and electron microscopic examination reveals the details of this pathological process directly at the tissue level.

The clinical part of the presented scientific work was performed in the Department of Pediatric Surgery of, Azerbaijan Medical University, histological and electron microscopic examination of biopsies in the Department of Histology, Cytology and Embryology and in the Electron Microscopy Laboratory of the Scientific Research Center of Azerbaijan Medical University biochemical examination of hormones and metabolites in the Biochemistry department and in Clinical Biochemistry Laboratory.

Examinations of patients included in the study, as well as healthy children included in the control group were carried out according to the following plan:

- General examination methods (anamnesis, examination, palpation, etc.)
- General analysis of blood, coagulogram, infections
- X-Ray of the chest
- Hormonal tests (determination of LH, FSH, and testosterone in the blood)
- Dynamic examination of connective tissue metabolites (OP, GAG) in blood and urine.
- Histological and electron microscopic examinations (examination of biopstat taken from the gubernaculum)
- US examination of the groin area and testicles

The materials and methods of the study consisted of 90 children aged 1-14. The results were compared with the performance of 25 practically healthy children included in the control group. The assessment of children by age was based on the WHO age classification. Thus, 4 age groups were used in our study: early childhood 1-3 years, I childhood 4-7 years, II childhood 8-11 years, adolescence 12-15 years. The main group included 60 children admitted to the clinic with a diagnosis of cryptorchidism. 27 (45%) patients included in the main group, belonged to the 1-3 age group, 20 (33.3%) to 4-7, 11 (18.3%) to 8-11, 2 (3, 3%) were included to the 12-15 age group. The mean age in this group was 4.82 ± 0.38 . 21 patients in the main group, had bilateral and 39 had unilateral (19 right, 20 left) cryptorchidism. The method of orchiopexy in the main group was determined by the location of the testis.

The localization of the testes was determined by palpation of the groin area and ultrasonography (US). The division was performed according to the upper 1/3 of the inguinal region (deep inguinal ring), the middle 1/3 (middle level of the inguinal canal) and the lower 1/3 (superficial inguinal ring and the entrance of the scrotum). In the main

group in unilateral patients the Bianchi method was performed, in 30.7% of cases and in 69.2% of cases, the standard method of orchiopexy was performed. This is due to the fact that in the main group the testes is often located in high position. In the same group in bilateral patients, Bianchi was performed in 57.1% of cases, standard orchiopexy in 28.5%. But in 14.2% of cases, in one side Bianchi and in another side standard orchiopexy was performed.

The relapsed group included 30 children who underwent orchiopexy surgery but recurred for 1 year or more. Most of these patients underwent orchiopexy surgery in the regions and a small number in private clinics in Baku, but due to repeated retraction of the testis, they re-applied to the clinic for surgery. In both groups, in addition to surgery, patients were prescribed magnesium (500 mg) and vitamin C (cevicap). Since these drugs are widely used in CT dysplasia, we have also preferred these medicines.^{6,7}

The majority of children in the relapsed group were in the 4-7 and 8-11 age groups. Thus, 13 patients separately were included in these age groups. The number of patients in early childhood in this group was 1, and the number of patients in adolescence was 3. 73.3% of children in the relapsed group had unilateral cryptorchidism (9 patients on the right, 13 patients on the left) and 8 patients bilateral cryptorchidism. In the relapsed group, 81.81% of patients with unilateral cryptorchidism performed standard, 18.19% performed Bianchi method, 62.5% of patients with bilateral cryptorchidism performed standard, 37.5% Bianchi method of orchiopexy.

⁶Avtandilov, A. Dzeranova K., Borovaya T., Didenko L. Effect of magnesium orotate on connective tissue matrix and cardiac inotropic function in patients with mitral valve prolapse. Clinical and morphological study / A. Avtandilov, K. Dzeranova, T. Borovaya [et al.] // Rational Pharmacotherapy in Cardiology, - 2013. vol. 9. № 4, - p. 390-397.

⁷Kalinin R., Suchkov I., Pshennikov A. et al. Application of Magnesium Drugs and Their Influence on the Indicators of Connective Tissue Dysplasia in Patients with Varicose Veins // Novosti Khirurgii, 2018, v. 26, No 1, pp.51-59

The majority of children included in the control group, - 54.2%, were included in the 4-7 age group. The children included in the control group were practically healthy children and had not undergone any surgery. Objective examination showed no signs of connective tissue dysplasia in these children.

In addition, 20 of the 60 patients who were included in the main group and underwent orchiopexy surgery at our clinic were called back to the clinic after 1-1.5 years and underwent re-examinations. In children who underwent re-examination, the testes were noted in the scrotum after surgery and no recurrence occurred. These children were placed in the treatment group.

The children were prescribed a 2-day diet while examining the CT metabolites in the blood and urine. Both CT metabolites and hormonal parameters were tested before breakfast.

RESEARCH RESULTS AND DISCUSSION

Examination of blood GAG levels by group showed that patients in both the main and relapsed groups had higher GAG levels than healthy children. In both groups, this figure is higher in bilateral patients than in unilateral patients.

Thus, in bilateral patients in relapsed group, the GAG was statistically reliable compared to children in the control group ($p < 0.001$) and increased 2.2 times, statistically unreliable compared to unilateral patients in the same group ($p > 0.05$) and increased 12%, was statistically significant ($p < 0.05$) and increased by 18% compared to bilateral patients in main group. In unilateral patients in the relapsed group, this indicator was statistically significant ($p < 0.05$) and increased by 16% compared to the corresponding patients in the main group. As can be seen, the maximum rate of GAG was observed in patients with bilateral relapsed patients. GAG is a carbohydrate part of proteoglycans, which are the main component of CT-intercellular substance. Elevated levels of this metabolite in the blood indicate that the breakdown of proteoglycans in the body is accelerated in patients

with cryptorchidism. On the other hand, GAGs inside of the gubernaculum, play a main role in expansion of this ligament and the descent of the testis into the scrotum. Thus, the gubernaculum goes through two stages of development: growth and regression. During the growth phase, the gubernaculum rapidly "swells". During this process, the inguinal canal widens and opens the way for the testis to descend. At this stage swelling of gubernaculum is associated with an increase in vascular permeability and the density of the GAGs it contains. Thus, GAGs are hydrophilic, increase their volume by attracting water, and due to this, the gubernaculum swells and expands. In patients with cryptorchidism, the increased level of GAG in the blood is proportional to its volume in the gubernaculum. On the other hand, the high volume of GAG in the gubernaculum in patients with cryptorchidism has been proved once again by our study of biopsies with electron and light microscopy. In general, the level of GAG was higher in all cryptorchid patients we studied. This indicator is higher in bilateral patients than in unilateral patients, and in patients with relapsed than the main group.

Examination of free OP in the blood also showed that in patients with bilateral cryptorchidism in the relapsed group, this figure is higher than in children in the other groups. Thus, the level of free OP in the blood of bilateral patients in the relapsed group compared to children in the control group was statistically reliable ($p < 0.001$) and increased 2.71 times, compared to unilateral patients in the same group statistically reliable ($p < 0.05$) and increased 26%, was statistically significant ($p < 0.05$) and increased by 23% compared to bilateral patients in the main group. In unilateral patients in the relapsed group, this indicator was statistically significant ($p < 0.001$) and increased by 49% compared to the corresponding patients in the main group.

Determination of total OP in the blood also showed that in patients with bilateral cryptorchidism in the relapsed group, this figure is higher than in children in the other groups. Thus, the level of total OP in the blood of bilateral patients in the relapsed group compared to

children in the control group was statistically reliable ($p < 0.001$) and increased 2.14 times, compared to unilateral patients in the same group statistically unreliable ($p > 0.05$) but increased 16%, was statistically significant ($p < 0.05$) and increased by 41% compared to bilateral patients in the main group. In unilateral patients in the relapsed group, this indicator was statistically significant ($p < 0.001$) and increased by 44% compared to the corresponding patients in the main group.

As we know, the indicator of free and total OP in the blood and urine is the breakdown product of collagen, which has a wide diagnostic criteria in CT pathologies. As mentioned above, the second stage of gubernaculum development is its regression stage. During this period, the size of the gubernaculum decreases and becomes a string-shaped ligament composed mostly of collagen fibers. In children with cryptorchidism, small amounts of collagen fibers are found in the gubernaculum. High levels of free and total OP in the blood and urine are a sign of rapid collagen metabolism. That is why children diagnosed with cryptorchidism have low levels of collagen fibers in the gubernaculum. Degenerative changes in the collagen fibers of the gubernaculum in patients with cryptorchidism were studied by us under the electron and light microscope, and the dissertation provides detailed information about this. It is no coincidence that during bilateral and relapsed cryptorchidism, these metabolites are higher in the blood.

According to the statistics of the world literature, the retraction of the testis after orchiopexy surgery appears about 13%. The reason for the retraction is the failure to perform a technically and tactically correct operation. In general, the status of CT in recurrent cryptorchidism has not been studied so far. Our study found that the level of CT metabolites are high in the blood and urine during cryptorchidism. Even in relapsed cryptorchidism, this figure is more higher. This suggests that CT dysplasia is also the cause of testicular retraction after orchiopexy surgery.

The level of blood testosterone was found to be minimal in bilateral relapsed patients than other groups. Thus, the level of total testosterone in the blood of bilateral patients in the relapsed group compared to children in the control group was statistically reliable ($p < 0.001$) and decreased 12.24 times, compared to unilateral patients in the same group also statistically reliable ($p < 0.001$) and decreased 6.66 times, was statistically significant ($p < 0.001$) and decreased by 2.85 times compared to bilateral patients in the main group. In unilateral patients in the relapsed group, this indicator was statistically unreliable ($p > 0.05$) and decreased by 19% compared to the corresponding patients in the main group.

In unilateral cryptorchidism, the testosterone level in the blood is restored at the expense of another healthy testis, but in bilateral cryptorchidism, this is not possible because both testes undergo pathological processes. On the other hand, we link the very low level of testosterone in relapsed bilateral cryptorchidism due to the operation performed on the testicle and repeated retraction. Although testosterone was low, it did not drop to "0" in any of the patients. This indicates that the testes are active and can perform their function

Examination of LH level in the blood shows that this indicator is the lowest in bilateral patients relapsed cryptorchidism group. In the control group, this figure is as high as expected. Thus, the level of LH in the blood of bilateral patients in the relapsed group compared to children in the control group was statistically reliable ($p < 0.001$) and decreased 10 times, compared to unilateral patients in the same group also statistically reliable ($p < 0.001$) and decreased 4.51 times, was statistically significant ($p < 0.01$) and decreased by 56% compared to bilateral patients in the main group. In unilateral patients in the relapsed group, this indicator was statistically unreliable ($p > 0.05$) and decreased by 17% compared to the corresponding patients in the main group.

Examination of FSH in the blood shows that the level of this metabolite in the blood of bilateral patients in the relapsed group

compared to children in the control group was statistically reliable ($p < 0.001$) and decreased 3.72 times, compared to unilateral patients in the same group also statistically reliable ($p < 0,05$) and decreased 97 %, was statistically significant ($p < 0.01$) and decreased by 60% compared to bilateral patients in the main group. In unilateral patients in the relapsed group, this indicator was statistically unreliable ($p > 0,05$) and decreased by 18% compared to the corresponding patients in the main group.

It is known that the hormones FSH, LH and testosterone affect spermatogenesis in different ways. Thus, testosterone, synthesized by the Leydig cells of the testis, promotes the growth and division of germ cells involved in the formation of sperm. Luteinizing hormone, synthesized from the anterior pituitary gland, stimulates Leydig cells to secrete testosterone. While the follicle-stimulating hormone, synthesized from the anterior pituitary gland, stimulates Sertoli cells. Without this stimulation, the germ cells will not turn into sperm. Although FSH and LH in patients in both the primary and relapsed groups were lower than in healthy children in the control group, they were generally below compare with the literature norm. Because patients with cryptorchidism usually do not have a problem with the pituitary gland and the amount of gonadotropic hormones are normal. If the level of gonadotropic hormones was low at the time of the examination, then we would link the low level of testosterone with cryptorchidism. In the present case, we associate low testosterone level with environmental factors that affect the testis because it remains outside the scrotum.

To record changes in the testes, the volume of the testes was determined ultrasonographically in all groups and compared with other patients.

It was found that the pathological testis of patients in both the primary and recurrent groups were smaller than those of other normal testis. In patients with bilateral cryptorchidism, the volume of both testes were small than norm. Thus, the volume of the right testis in

patients with right-sided cryptorchidism in the main group was 25.33% smaller than the left testis (healthy) ($p < 0.001$). The volume of the left testis in patients with left-sided cryptorchidism in this group was 32.72% smaller than the right testis (healthy) ($p < 0.001$). Both testes of patients with bilateral cryptorchidism in this group are smaller than the same age group children's testes, but almost the same size compare with each other. The size of the testes in the patients in the control group was in accordance with the literature.

The volume of the right testis in patients with right-sided cryptorchidism in the relapsed group was 35.22% smaller than the left testicle (healthy) ($p < 0.01$). The volume of the left testis in patients with left-sided cryptorchidism in this group was 30.55% smaller than the right testis (healthy) ($p < 0.01$). The volume of both testes of patients with bilateral cryptorchidism in this group are smaller than the same age group children's testes, but almost the same size compare with each other. In both groups, the volume of the affected testis is small, and this is an expected result. Because the testis does not descend into the scrotum in time, its size is smaller than that of other testis due to the disruption of its normal development and the influence of environmental factors. Surgery performed during relapsed cryptorchidism and repeated retraction has a more negative impact on the development of the testicle. That is why the volume of the testis in the relapsed group is even smaller than in the main group

CT metabolites, as well as hormonal indicators, were re-tested in children with clinical recovery to maintain dynamic control. Repeated scrotal US examinations were also performed in recovered children to determine the testicular volume increase. It was found that in patients treated with unilateral cryptorchidism, the average level of GAG after 1 year treatment period was statistically reliable ($p < 0.001$) and decreased by 37% compared to the pre-operative and pre-treatment index of these patients. Although before treatment this figure increased by 69% compared to control group, this increase fell to 24% after treatment, but it is not statistically significant ($p > 0.05$).

Bilateral patients also show a decrease in GAG level after treatment. Thus, in post-treatment children, this indicator was statistically reliable ($p < 0.001$) compared to pre-treatment children and decreased by 26%. Although before treatment this figure increased by 82% compared to control group, this increase was 45% after treatment.

Table 1

Connective tissue metabolites in recovery and in the control groups

Indicators	Recovery group (n=20)				Control group (n=25)
	Unilateral cryptorchidism (n=14)		Bilateral cryptorchidism (n=6)		
	before treatment	after treatment	before treatment	after treatment	
GAG ng/ml	4,47±0,31 (1,9-6,3) p <0,001	3,27±0,37 (1,9-6,3) p >0,05 p ₁ <0,001	4,82±0,71 (3,20-7,70) p <0,05 p ₂ >0,05	3,84±0,46 (2,63-5,9) p <0,05 p ₁ <0,001 p ₂ >0,05	2,64±0,17 (1,40-5,70)
Free OP (blood) mkM/l	15,1±2,03 (3,8-30,0) p <0,05	11,6±1,17 (3,7-20,0) p >0,05 p ₁ <0,05	23,2±2,46 (15,0-32,0) p <0,01 p ₂ <0,05	15,1±2,15 (8,33-22,4) p >0,05 p ₁ <0,05 p ₂ >0,05	10,0±0,46 (5,82-15,19)
Total OP (urine) mmol/l	255,6±18,3 (164,3-457,0) p <0,01	205,9±10,8 (152,0-303,0) p >0,05 p ₁ <0,01	317,2±44,9 (215,0-501,0) p <0,01 p ₂ >0,05	229,2±34,0 (186,0-398,3) p >0,05 p ₁ <0,01 p ₂ >0,05	193,1±11,0 (99,7±331,5)

Note: p - statistical accuracy of the difference relative to a healthy group indicator;
 p₁ - statistical accuracy of the difference compared to the pre-treatment indicator;
 p₂ is the statistical accuracy of the difference compared to those with unilateral cryptorchidism in the group.

In the postoperative period, free OP in the blood, as well as the total OP in the urine, showed a corresponding change in the level of GAG in the blood of patients in this group. Thus, in both unilateral

and bilateral patients in the postoperative period, these indicators decreased compared to pre-treatment.

Table 2

Hormonal indicators in recovery and in the control groups

Indicators	Recovery group (n=18)				Control group (n=25)
	Unilateral cryptorchidism (n=12)		Bilateral cryptorchidism (n=6)		
	before treatment	after treatment	before treatment	after treatment	
testosterone ng/dl	2,43±0,253 (0,70-4,00) p <0,001	3,06±0,265 (1,20-4,50) p <0,05 p ₁ <0,001	0,83±0,056 (0,70-1,00) p <0,001 p ₂ <0,001	1,22±0,270 (0,50-2,10) p <0,001 p ₁ >0,05 p ₂ <0,001	3,82±0,171 (2,80-5,00)
LH mIU/ml	0,59±0,098 (0,15-1,20) p <0,01	0,81±0,147 (0,30-2,00) p >0,05 p ₁ <0,05	0,15±0,032 (0,10-0,30) p <0,001 p ₂ <0,01	0,25±0,034 (0,10-0,32) p <0,001 p ₁ >0,05 p ₂ <0,01	1,16±0,098 (0,40-2,00)
FSH mIU/ml	1,89±0,266 (0,70-3,50) p <0,01	2,58±0,318 (1,10-5,00) p >0,05 p ₁ <0,01	1,11±0,209 (0,76-2,10) p <0,001 p ₂ <0,05	1,74±0,145 (1,15-2,10) p <0,01 p ₁ <0,05 p ₂ <0,05	3,24±0,279 (0,90-5,60)

Note: p - statistical accuracy of the difference relative to a healthy group indicator;
 p₁ - statistical accuracy of the difference compared to the pre-treatment indicator;
 p₂ is the statistical accuracy of the difference compared to those with unilateral cryptorchidism in the group.

Hormonal changes were also expected in children who recovered. In patients treated with unilateral cryptorchidism, the mean level of testosterone after 1 year treatment period was statistically reliable (p <0.001) and increased by 24% compared with the preoperative and pre-treatment index of these patients. Although before treatment this figure decreased by 57% compared to control group, this decrease fell to 25% after treatment, and was statistically

reliable ($p < 0.05$). Bilateral patients also showed an increase in testosterone after treatment. Thus, in post-treatment children, this indicator was statistically unreliable ($p > 0.05$) compared to pre-treatment children and increased by 46%. Although before treatment this figure decreased 4.52 times compared to control group, this decrease was 3.14 after treatment. After treatment, the minimum testosterone level was 1.2 ng / ml and the maximum was 4.50 ng / ml in unilateral patients. In bilateral patients, this figure was 0.5 ng / ml and 2.1 ng / ml.

In the postoperative period, the level of LH in the blood, as well as the level of FSH, showed a corresponding change in the level of testosterone in the blood of patients in this group. Thus, in both unilateral and bilateral patients, these indicators increased in the postoperative period compared to pre-treatment.

Scrotal US examination of recovered children showed that in patients with right-sided cryptorchidism, the size of the right testis increased 10.9% compared with pre-treatment period but was statistically unreliable. In left-sided cryptorchidism, compared the post-treatment period with pre-treatment time, the volume of testis increased by 22.7% but not statistically reliable. In patients with bilateral cryptorchidism, a comparison of the postoperative period with the previous period showed that both testes showed statistically reliable results, the right testicle increased in size by 37% and the left testicle by 26.7%.

Thus, the determination of CT metabolites in biological fluids, as well as light and electron microscopic examination of biopsies taken from the gubernaculum, give us reason to believe that there has been a fundamental change in connective tissue during cryptorchidism. The study of changes in connective tissue, of course, increases the relevance of conservative treatment in the correction of CT dysplasia to prevent the subsequent retraction of the testis, along with orchiopexy surgery during cryptorchidism. Samples taken from the blood and urine of patients with cryptorchidism showed high levels of

free and total OP, as well as GAG. It was also found that these rates were even higher in children with recurrent cryptorchidism than in the main group. In addition to the high content of CT metabolites in the body fluids, light and electron microscopic examination of biopsies taken from the gubernaculum in patients with cryptorchidism showed high levels of GAG in the tissue in parallel with the excess in the body fluids. In addition, electron microscopic examination revealed that collagen fibers in the gubernaculum were exposed to destructive changes observed by defibrillation. Of course, this change in collagen fibers also reduces the mechanical capacity of the gubernaculum. As a result, the process of testis descending is disrupted without beginning sclerotic changes in the gubernaculum. In view of all this, in addition to the orchiopexy surgery performed on patients, Magnerot (magnesium) and Cevicap (vitamin c) drugs were prescribed in the postoperative period. We prefer Magnerot because it is a widely used drug in differentiated and non-differentiated CT diseases. Cevicap contains vitamin C. Vitamin C plays an indispensable role in the formation of oxyproline, which is involved in the synthesis of collagen. Collagen synthesis increases during vitamin C intake, postoperative wound healing is accelerated, and rough scar tissue does not form in the postoperative period. On the other hand, vitamin C helps in the synthesis of collagen, which is necessary for the formation of healthy connective tissue. Due to this, a thin, healthy collagen-rich scar tissue is formed. No recurrent was observed after conservative treatment with surgery in patients with high levels of CT metabolites in both the primary and relapsed groups.

In our study, in addition to CT metabolites, the ultrasonographic volume of the testes and changes in hormonal status were also reflected. It was found that the late performance of the orchiopexy operation affected to the volume of the testis. Thus, the fact that the testis remained in the inguinal canal for a long time resulted in a decrease on its volume. From hormonal indicators especially the decrease in the concentration of testosterone is attracts attention.

Although the concentration of FSH and LH from other hormones decreases, these indicators can be considered as low levels of the norm. The change in testosterone levels is directly related to the processes that take place in the testicular tissue. This is further evidenced by the fact that this figure is even lower in patients with recurrent bilateral cryptorchidism.

Thus, no recurrence occurred in any patient after our treatment and surgery, and positive dynamics was observed in all patients in CT metabolite parameters, hormonal indicators in the blood, ultrasonographic measurements of the testes. This suggests that CT dysplasia in patients with cryptorchidism must be investigated, and if pathology occurs in this system, along with orchiopexy surgery, CT dysplasia must be corrected to minimize postoperative retraction.

Results

1. During unilateral cryptorchidism, the level of GAG in the blood increased by 69% ($p < 0,001$) compared with the control group, the indicator of free oxyproline in the blood by 44% ($p < 0,001$), the indicator of total oxyproline in the urine by 28% ($p < 0,001$). During bilateral cryptorchidism, the level of GAG in the blood increased by 87% ($p < 0,001$) compared with the control group, the indicator of free oxyproline in the blood by 2.2 times ($p < 0,001$), the indicator of total oxyproline in the urine by 51% ($p < 0,001$) [6, s.21].

2. During unilateral relapsed cryptorchidism, the level of GAG in the blood increased by 96% ($p < 0,001$) compared with the control group, the indicator of free oxyproline in the blood by 2.15 times ($p < 0,001$), the indicator of total oxyproline in the urine by 85% ($p < 0,001$). During bilateral relapsed cryptorchidism, the level of GAG in the blood increased by 2.2 times ($p < 0,001$) compared with the control group, the indicator of free oxyproline in the blood by 2.71 times ($p < 0,001$), the indicator of total oxyproline in the urine by 2.14 times ($p < 0,001$) [4, s.62; 8, s.58].

3. From hormones, a significant change was noted, especially in the level of testosterone (a decrease by 13.2 times ($p < 0.001$)) in patients with bilateral relapsed cryptorchidism compared with the

control group, and by 4.6 times ($p < 0.001$) in patients with bilateral cryptorchidism). In both recurrent and main group patients, a decrease in the volume of the testes remaining in the inguinal canal is noted, compared with a normal descended testis it was statistically reliable. In patients with bilateral cryptorchidism, the size of both testes is smaller than in the control group [7, s.72; 10, s.11].

4. Due to the effect of edema fluid formed as a result of the increase of the vascular permeability during cryptorchidism, in the histotopography of the collagen fibers themselves and their groups formed with their participation, disruption of their structures of various degrees and formation of degenerative changes in the collagen fibers were found in the electronic microscopic study of biopsy samples taken from the gubernaculum [11, s.59-60].

5. It is more appropriate to do standart orchiopexy in testis which located in inguinal canal, and perform Bianchi method orchiopexy in testis which located outside of the inguinal canal and at the entrance of the scrotum. In patients with high level of CT metabolites, the use of vitamin C and magnesium along with orchiopexy surgery prevented relapses, and a decrease in metabolite parameters was observed in the postoperative period [4, s.42].

PRACTICAL RECOMMENDATIONS

1. Determination of CT metabolites in the blood and urine in patients with cryptorchidism, give information on CT dysplasia in these patients.

2. In patients with high level of CT metabolites, conservative treatment along with orchiopexy surgery may help prevent testicular retraction.

3. It is more appropriate to do transverse incision in testis which located in inguinal canal, and scrotal incision in testis which located outside of the inguinal canal and at the entrance of the scrotum

4. In case of inguinal cryptorchidism, it is better to give up hormonal treatment and prefer orchiopexy surgery.

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NOMINAL REDUCTIONS

AR-androgen receptor

CT - connective tissue

FSH - follicle stimulating hormone

GAG - glycosaminoglycans

LH - luteinizing hormone

OP - oxyproline

US - ultrasound

CHG - chorionic gonadotropin

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