

ANNOTATION

PhD thesis by **Sagymbayeva Assel**

on the topic « **Improved approach to treatment and metaphylaxis of obturating stones of the upper urinary tract in children**», submitted for the of Doctor of Philosophy (Ph.D.) degree in doctoral program 8D10103 – «Medicine»

Relevance of the research topic

Currently, nephrolithiasis is a common pathology in pediatric urologic practice, which makes its study particularly relevant. In Central Asia, this pathological process accounts for approximately 65-70% of cases of pediatric surgical diseases (Azizov A.A. et al. 2000, Riazentsev V.E. et al. 2013, Apolikhin O.I. et al. 2016). Moreover, this disease in 99% of cases is accompanied by inflammatory changes in the urinary system, such as calculous pyelonephritis, calculous hydronephrosis, ureterohydronephrosis, pyonephrosis, paranephritis, cystitis, and urethritis, which require a comprehensive approach to treatment (Ahmad I. 2013, Bagga H.S. et al 2013).

Approximately 40% of all congenital developmental anomalies are related to the urinary system. Of these, 2/3 of the anomalies are significant causative factors contributing to the development of various pathologic processes such as pyelonephritis and nephrolithiasis (Iglova YA, et al. 2011, Riccabona M, Avni FE, Blickman JG, et al. 2008). Stones in the urinary tract, formed against the background of congenital anomalies, regardless of their size, shape, number and location, exacerbate the violation of urodynamics, which often leads to irreversible functional and structural changes in the urinary system. Therefore, it is important to conduct a detailed study of each patient and consider all these factors when choosing a treatment method.

With the development of new technologies in modern medicine and, in particular, in urology, in recent years, the approach to the diagnosis of nephrolithiasis, methods of conservative and surgical treatment, as well as prevention and metaphylaxis of stone formation in the urinary system have changed radically.

In addition, it is important to consider the age and body weight of the children when choosing a treatment method. Stones in the urinary tract formed against the background of congenital anomalies, regardless of their size, shape, number, and location, aggravate urodynamic disorders, which often lead to irreversible functional and structural changes in the urinary system. In this regard, it becomes especially important to search for new methods of diagnosis and optimization of existing methods of surgical correction and management of patients with nephrolithiasis against the background of congenital anomalies of kidney development.

There is insufficient information in the literature on the choice of treatment methods for complicated (obturating) nephrolithiasis, and the variety of variants of stone localization in the urinary system, the duration of the disease and the degree of renal dysfunction have not been considered (De S. et al. 2015, He Q., et al. 2019).

Nevertheless, despite extensive research, to date, there are still many unresolved issues concerning the diagnosis and tactics of surgical correction of nephrolithiasis with

anomalies of the urinary system, the choice of methods of restorative treatment, and metaphylaxis (Wright A. et al. 2016).

In addition, in the literature sources, there is mixed information about the prevention of stone formation and metaphylaxis of nephrolithiasis in children in the postoperative period, which predetermines the importance of the studied problem for modern medical science and practical health care.

The aim of the dissertation research: to improve the results of treatment and metaphylaxis in children with obturating stones of the upper urinary tract.

Objectives of the study

1. To investigate the microbial profile of urine in children with obturating upper urinary tract stones.
2. To develop indications and contraindications to fibropyelocalicolithoextraction from mini lumbotomy access in nephrolithiasis.
3. To perform a comparative analysis of the results of open pyelolithotomy with reconstructive correction of the pyeloureteral segment of the urinary tract and fibropyelocalicolithoextraction for nephrolithiasis in children.
4. To develop an optimal algorithm for nephrolithiasis metaphylaxis in children based on urine urease activity test.

Methods of the investigation: The single-stage, retro-, and prospective study was conducted in 3 stages by methods of continuous and random sampling, case-control, on the volume of 244 observations at the age of 3 months to 18 years.

All patients were examined according to the standard plan, including: anamnesis collection, objective examination, general clinical and laboratory examination, complex ultrasound examination of the abdominal cavity and urinary system organs, intravenous urography, and computed tomography (CT) of retroperitoneal organs. In each clinical case, the following data were evaluated: the size of stones, their number, localization, the degree of involvement of different parts of the calyx system, and the location of the pelvis (intra-, extra-, mixed). The examination performed before treatment of patients also included electrocardiography, general and biochemical blood and urine tests, coagulogram, and bacteriologic seeding of urine. The studies were conducted according to standard methods.

We also carried out special urine studies 1 month after surgical interventions, which included determination of urine urease activity (UA); stability of urine pH; urine crystal formation ability; crystal formation test.

Methods of surgical treatment:

- Open pyelolithotomy with lithoextraction and reconstructive correction of the pyeloureteral segment of the urinary tract;
- Fibropyelocalicolithoextraction from the mini lumbotomy access.

Object of the study: children with nephrolithiasis requiring surgical treatment.

Subject of the study: studying the effectiveness of a new method - fibropyelocalicolithoextraction; special methods of urine tests (urease activity, pH stability, the ability of urine to crystal formation, crystal formation test).

The study was conducted at the JSC «Scientific Center of Pediatrics and Children's Surgery» in Almaty from 2015 to 2023. The study was approved by the local ethical committee of the NAO «Kazakh National Medical University S.D. Asfendiyarov» (protocol number 1102) and was conducted in accordance with the international rules of «Good Clinical Practice» and with the guidelines and ethical standards set forth in the 1964 Declaration of Helsinki, as last modified at the 64th General Assembly of the WMA, Fortaleza, Brazil, October 2013.

Depending on the objectives of the study, groups and subgroups of children were identified.

At stage 1, a retrospective analysis of 204 children admitted with the diagnosis of urolithiasis to the urology department of the JSC «Scientific Center for Pediatrics and Children's Surgery» in the period 2015-2021 was performed.

At stage 2, in accordance with the objective of our study, a comparative assessment of the clinical efficacy of open pyelolithotomy with reconstructive correction of the pyeloureteral segment and application of fibropyelocalicolithoextraction from mini lumbotomy access for nephrolithiasis in children was performed. A single-stage study was conducted by random sampling in 58 patients with obturating upper urinary tract stones. Of the 58 children, Group 1 - 32 patients (recruited retrospectively) underwent open surgery, Group 2 - the remaining 26 children (recruited prospectively) underwent a new method of calyx stone extraction using fibropyelocalicolithoextraction. These patients were recruited between January 2021 and April 2023.

At the 3rd stage, we studied the clinical efficacy of special methods of urine examination in 40 children with nephrolithiasis (1 - main group) and 40 conditionally healthy children (2 - control group) using the case-control method with group observation. Depending on the level of urine urease activity (UA), group 1 (children with nephrolithiasis) was divided into three subgroups (subgroup 1 - low UA, subgroup 2 - medium UA, subgroup 3 - high UA). These patients were recruited between September 2021 and June 2023.

Inclusion criteria:

- Children with obturating upper urinary tract stones with combined hydronephrosis between 3 months to 18 years of age participated in the study;
- Completion of a follow-up examination after a specified time to evaluate the effectiveness of the treatment.
- Informed consent confirming participation in the study.

Exclusion criteria:

- Patients with nephrolithiasis not requiring surgical treatment.
- Patients with multiple malformations
- Patients with staghorn stones
- Patients with CKD, including those with CKD
- Patients with acute inflammatory processes
- Patients who refused to participate in the study.
- Failure to appear for follow-up examination

The main provisions of the defense

1. The study of urine microbial profile is the key for revealing the predictors of complicated course of nephrolithiasis that allows the application of rational methods of treatment in time.
2. The developed and implemented method of fibropyelocalicolithoextraction from mini lumbotomy access at nephrolithiasis in children proves high efficiency.
3. The use of fibropyelocalicolithoextraction significantly reduces the duration of surgery, intraoperative and postoperative complications, hospitalization time and significantly improves the quality of life of patients.
4. The study of urine urease activity test allows the development of an optimal algorithm for the metaphylaxis of nephrolithiasis in children.

Scientific novelty of the study

1. For the first time, indications and contraindications to the use of fibropyelocalicolithoextraction for nephrolithiasis in children were developed (Patent for invention - protection document № 36591 dated 09.02.2024. "Method of stones extraction from the kidney calyces in children).
2. The high clinical effectiveness of fibropyelocalicoscopy with lithoextraction from mini lumbotomy access in children with nephrolithiasis is proved.
3. The rationality of urine urease activity test application for the metaphylaxis of nephrolithiasis in children was substantiated for the first time.
4. The correlation between urease activity and the urine ability to crystals formation with the measurement of crystal formation rate was determined.
5. An algorithm for the metaphylaxis of nephrolithiasis in children was developed.

Practical significance

1. Assessment of urine microbial profile in patients with nephrolithiasis contributes to the prevention of infectious-inflammatory complications.
2. The obtained results of fibropyelocalicoscopy with lithoextraction from mini lumbotomy access allow improvement in the results of surgical interventions in children with nephrolithiasis, reduces the risk of postoperative complications, as well as reduces the time of hospitalization and recurrences in the distant period, which allows to introduce it more widely in clinical practice.
3. Special methods of urine examination are not expensive from a financial point of view and can be used in any laboratory of medical institutions.
4. The developed algorithm of metaphylaxis allows for its wider application in clinical practice in complex treatment and improvement of the quality of life of children with nephrolithiasis.

Personal contribution of the doctoral student

The doctoral student independently justified the research directions; created the research design and organization of all its stages; selected patients, data processing and analysis; designed, presented and discussed of the dissertation results. The doctoral

student personally formulated the goals, objectives of the study, the provisions put forward for defense; introduced a new method of extraction of stones from the calyces of the kidney in children; developed and implemented the algorithm of metaphylaxis nephrolithiasis in children. The prospective observation of patients participating in the study, creation of the database, formulation of conclusions and practical recommendations, writing chapters of the dissertation work, preparation of the main publications, implementation of the results of the study in practice belongs to the doctoral student personally.

Conclusions:

1. The urine microbial profile in children with nephrolithiasis was marked by the predominance of uropathogens such as *Escherichia coli* 49 (32%), *Enterococcus faecalis* 17 (11.1%) and a combination of two or more pathogenic agents 32 (20.9%), with three-component associative forms of microorganisms manifested in 4 cases (2.3%) in purulent forms of pyelonephritis.
2. Indications for fibropyelocalicolithoextraction are stones of the calyx-pelvis system up to 20 mm in size combined with stenosis of the pyeloureteral segment. Absolute contraindications to fibropyelocalicolithoextraction include exacerbation of calculous pyelonephritis, acute kidney injury.
3. The effectiveness of using open intervention in children of group 1 was 87% ($p>0,05$), whereas the method we proposed - fibropyelocalicolithoextraction from mini lumbotomy access, as well as with the use of metaphylaxis algorithm showed statistically significant treatment results in children of group 2 ("stone free rate" was 96% ($p>0,05$)).
4. A very high correlation between urease activity and urine crystal formation ability with the measurement of crystal formation rate was proved ($p=0.997$), which allowed the development of optimal algorithm for the metaphylaxis of nephrolithiasis in children.

Approbation of the results of the dissertation

The main provisions of the dissertation work were presented:

1. III Congress of pediatric surgeons, anesthesiologist-reanimatologists of the Republic of Tajikistan «Modern aspects of pediatric surgery and intensive care issues: achievements, problems and ways to solve them». Dushanbe, Republic of Tajikistan, 20 November, 2020 (online).
2. IX Congress of Children's Doctors of Kazakhstan «Achievements and prospects of development of pediatrics and pediatric surgery» Forum of young scientists for doctoral students, master's students and residents «Young researcher: challenges and prospects of development of modern pediatrics and pediatric surgery». Almaty, Republic of Kazakhstan, 23 April, 2021.
3. X Jubilee All-Russian School on pediatric urology. Moscow, Russian Federation, 7 April, 2022.

4. International Scientific and Practical Conference «Young researcher: challenges and prospects of development of modern pediatrics and pediatric surgery», dedicated to the memory of pediatric surgeon, Doctor of Medical Sciences Akhparov Nurlan Nurkinovich. Almaty, Republic of Kazakhstan, April 22, 2022.
5. Global Summit on Nephrology, Urology and Kidney Transplantation. Zurich, Switzerland, 15 June, 2022 (online).
6. International Scientific and Practical Conference «Pediatrics of Kazakhstan: everything, today and forever» dedicated to the 90th anniversary of the Scientific Center of Pediatrics and Children's Surgery. Almaty, Republic of Kazakhstan, October 6-7, 2022.
7. 7th World Congress of pediatric surgery. Prague, Czech Republic, October 12-15, 2022 (online).
8. The Global Health Network Conference. Cape Town, South Africa, November 25, 2022 (online).
9. XI All-Russian School of Pediatric Urology, Moscow, Russian Federation, April 6-7, 2023.
10. 1st International «Asfen.Forum, New Generation-2023», Almaty, Republic of Kazakhstan, June 5-6, 2023.
11. X Anniversary Congress of Pediatricians of CIS countries «Child and Society: Problems of Health, Development and Nutrition» and II Congress of Pediatric Surgeons of Central Asia, Kyrgyz Republic, Issyk-Kul, September 14-16, 2023.
12. Scientific-practical conference of young scientists, doctoral students, master's students and residents «Young researcher: challenges and prospects of development of modern pediatrics and pediatric surgery», Almaty, Republic of Kazakhstan, October 13, 2023.

Information about the implementation

The method of determining the urease activity of urine and testing for crystal formation in children with nephrolithiasis was implemented in the practice of the department of «Clinical Diagnostic Laboratory» JSC «Scientific Center for Pediatrics and Children's Surgery» Almaty, Republic of Kazakhstan (acts of implementation) (Appendix A, B).

«Method of stones extraction from the kidney calyces in children» is implemented in the practice of the Department of Urology of JSC "Scientific Center of Pediatrics and Children's Surgery" Almaty, Republic of Kazakhstan (act of introduction of March 13, 2023) (Appendix C).

«Algorithm of metaphylaxis of nephrolithiasis in children» is implemented in the practice of the Department of Urology of JSC «Scientific Center for Pediatrics and Children's Surgery» Almaty, Republic of Kazakhstan (act of implementation dated May 15, 2023) (Appendix D).

Publications

According to the results of the study, the author published 14 scientific papers, including the following:

- In the editions recommended by the Committee for Quality Assurance in Education and Science of the Ministry of Education and Science of the Republic of Kazakhstan – 3 articles;
- In international peer-reviewed journals with impact factor according to Journal Citation Reports, the percentile index of Cite Score 45 percentile in the Scopus database – 1 article;
- In the proceedings of international conferences – 10;
- Patent for invention - protection document № 36591 dated 09.02.2024. «Method of stones extraction from the kidney calyces in children».

Awards:

- Prize-winner in the 1st International Forum «Asfen.Forum, New Generation-2023» competition
- Winner of the republican competition in the nominations «Best Young Health Care Specialist – 2023», «For Contribution to Health Care – 2023».

The scope and structure of the dissertation

The dissertation consists of 125 pages of typewritten text and includes an introduction, literature review, a chapter describing the materials and methods of research, chapters of own research, conclusion, conclusions, practical recommendations, and a list of literature consisting of 173 sources, including 8 domestic and 165 foreign sources, appendices. The text contains 51 figures and 26 tables.