

Annotation

Of dissertations for the degree of Doctor of Philosophy (PhD)

"6D110100-Medicine" specialty

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on the topic "Improving the prevention of late postoperative complications in patients with benign prostatic hyperplasia"

The relevance of research. Benign prostatic hyperplasia (BPH) is the most common benign neoplasm in men over 40 years of age; it is diagnosed in approximately 8% of men in their fourth decade, 50% of men in their fifties, and 90% of men over 80 years of age (McVary 2006). BPH is characterized by changes in the size of the prostate, as well as clinical symptoms from the lower urinary tract in the form of obstruction (feeling of incomplete emptying of the bladder, weak urine flow) or irritation (dysuria, stranguria, frequent urination) [European Association 2004]. BPH may be asymptomatic, respond to lifestyle changes, or require medication or surgery; the severity of symptoms is directly correlated with age [Kapoor 2012]. In addition to age, the risk factors for the development of BPH include obesity, type 2 diabetes, high alcohol consumption and low physical activity [Lokeshwar 2019, Parsons 2009, Sarma 2012].

Treatment of BPH includes both a medical approach and surgery. Indications for surgical treatment of BPH include: ineffectiveness of drug therapy, refractory urinary retention, recurrent urinary tract infection, persistent hematuria, presence of bladder stones, and renal failure [Langan 2019]. The most commonly performed surgical procedure is transurethral resection of the prostate (TUR), which is considered the gold standard for BPH treatment. One of the late postoperative complications of surgical treatment of BPH is the development of urethral stricture or sclerosis of the bladder neck, which significantly worsens the quality of life of patients. Urethral stricture and sclerosis of the bladder neck are one of the most common urological pathologies in men in various countries. It is defined as narrowing of the urethral lumen, requiring interventions to improve the flow rate of urine.

The development of urethral strictures may be a consequence of excessive trauma to the mucous membrane during endoscopy of the bladder and the use of a resectoscope with the development of inflammatory reactions preceding surgical intervention or sclerotic changes in the urethral wall and the prostate itself due to the peculiarities of its morphological structure. This is also facilitated by productive inflammatory and granulation formations containing a large number of blood vessels, which increase the possibility of bleeding of the prostate bed after surgery [Favorito L 2017, King C 2019].

The main causes of strictures are caused by urethral fibrosis, due to sexually transmitted infections, pelvic injuries, and surgical interventions [Payne S., 2022; Wessells H., 2023]. The most complex urethral strictures that require radical treatment are strictures longer than 5 cm, posterior stenosis, the absence of previous lower urinary tract symptoms, and traumatic strictures [King C., 2019].

An increased risk of strictures is associated with the small size of the meatal canal [Mannem S. R., 2022]. In patients with a large prostate gland, the risk of developing postoperative urethral strictures increases, while the incidence rate increases to 19 % [Elsaqa M., 2023; Komura K., 2015]. Stenosis or sclerosis of the bladder neck is a long-term complication of surgical

interventions for benign prostatic hyperplasia. The overall incidence of this pathology is 1.3% after TURP, 0.66% after enucleation, and 1.2% after ablation [Castellani D., 2021].

The risk of developing urethral strictures and sclerotic changes in the bladder neck is associated with the presence of inflammatory diseases of the prostate, the type of surgery, the diameter of surgical instruments, the use of a urethral catheter, and a large prostate volume before surgery [Grechenkov A., 2018; Tao H., 2016].

One of the preventive methods of treatment aimed at preventing the development of late obstructive complications after surgery on the prostate gland is the use of antiproliferative medications that have a cytostatic effect. 5-fluorouracil is one of these drugs with high antimitotic activity, safety when applied topically, and relatively low cost. The results of its use in experimental studies on the prevention of urethral strictures in animals demonstrated its high effectiveness [Uyeturk 2014; Zhou 2021]. Currently, clinically, there are not enough clinical studies on the use of this drug to prevent the development of urethral strictures, which prompted us to evaluate its effectiveness.

The relevance of the research problem is due to the importance of timely detection of predictors of obstructive uropathy development in the late stages after surgical treatment of BPH, their early diagnosis, in order to prevent their development.

The study was approved by the Local Ethics Commission Государственного мof Semey State Medical University (now NAO "МУС") on December 28, 2018, Protocol No. 4. Each subject received informed consent to participate in the health study.

Purpose of the study. To scientifically substantiate and develop practical recommendations for improving the prevention of late obstructive complications after open adenectomy and transurethral resection in patients with benign prostatic hyperplasia.

Research objectives:

1. To assess the main risk factors for the development of late complications after open adenectomy and transurethral resection of benign prostatic hyperplasia.
2. To develop and implement a method for preventing the development of urethral stricture and sclerosis of the bladder neck after adenectomy and transurethral resection of the prostate gland.
3. To analyze the immediate and long-term results of the method of prevention of late complications after adenectomy and transurethral resection of the prostate gland.
4. To develop practical recommendations for the prevention of late obstructive postoperative complications after open adenectomy and transurethral resection in BPH.

Scientific novelty of the study:

1. For the first time, we evaluated risk factors for late obstructive postoperative complications in patients with BPH, calculated odds ratios for each risk factor, and determined predictors of the development of urethral stricture and bladder neck sclerosis within 6 months after surgery.
2. For the first time, a method for preventing strictures and sclerosis of the bladder neck in the early postoperative period was developed and used in a clinical study in the form of irrigation of the urethra and bladder with a solution of 5-fluorouracil using a modified three-way Foley urinary catheter. Received utility model patent No. 4223 dated 09.08.2019. "Three-way urinary catheter for drainage and washing of the bladder and urethra".
3. For the first time, the immediate and long-term results of using the method for preventing late complications after adenectomy and transurethral resection of the prostate gland were evaluated. The study group showed a statistically significant improvement in such indicators as a decrease in the number of obstructive uropathies formed, a decrease in IPSS scores, an

improvement in the quality of life, an improvement in erectile function, an increase in the maximum rate of urination, and a decrease in the volume of residual urine. A certificate of entering information in the State Register of Rights to Copyrighted Objects No. 42140 dated 18.01.2024 "Prevention of postoperative urethral strictures by irrigation with 5-fluorouracil through a modified urinary catheter" was obtained.

4. For the first time, based on the determination of the most significant predictors of the development of late obstructive postoperative complications and the results of a clinical study, recommendations for the management of patients undergoing surgical treatment for BPH were developed and implemented in practice.

Scientific and practical significance of the dissertation research:

Based on the study of domestic and foreign experiences of urological care for patients with benign prostatic hyperplasia, the results of using an improved method for the prevention of late complications after adenomectomy, and TUR, practical recommendations for improving measures for the prevention of postoperative complications in this cohort of patients were developed and proposed.

The results of the dissertation research were implemented in the work of the urology departments of the Semey Kidney Center medical Institution and the Semey Emergency Hospital (implementation certificates, Appendix).

The main risk factors for the development of obstructive uropathies in the long-term period after surgery in patients with BPH at the outpatient stage were determined with the calculation of the odds ratio for each risk, which made it possible to establish predictors of the occurrence of these complications.

Assessment of the development of late postoperative obstructive complications of BPH treatment includes laboratory and instrumental examination methods (uroflowmetry, transabdominal ultrasound of the prostate), as well as a questionnaire according to the IPSS scale with the definition of quality of life and the ICEF-5 questionnaire for analyzing the presence of erectile dysfunction.

Assessment of the risk of late postoperative obstructive complications based on the presence of established predictors (IPSS (scores), quality of life (scores), type of surgery, prostate size, uroflowmetry (ml/sec), residual urine (ml), age (years), BMI (kg/m²), leukocyturia (units in p/s), erythrocyturia (units in p/s) allows you to choose the preferred method of surgical intervention and preventive treatment (certificates of entry in the state register of rights to objects protected by copyright No. 42140 of 18.01.2024, No. 43486 of 05.03.2024).

A method of irrigation of the bladder and urethra with a solution of 5-fluorouracil using a modified three-way Foley urinary catheter was developed and implemented in practice, which showed high preventive effectiveness (utility model patent No. 4223 of 09.08.2019).

Recommendations for the management of patients undergoing surgical treatment for BPH with high risks of obstructive postoperative complications have been developed and implemented (acts of implementation, Appendix).

The results of the study are used in the educational process at the Department of Surgical Disciplines of the National Academy of Medical Sciences of the Russian Academy of Medical Sciences in the specialty "Urology" at all levels of educational activity when analyzing the topic "Benign prostatic hyperplasia".

Materials and methods of the study:

To achieve the goal and solve the tasks set, we have carried out the following research areas:

1 Research areas:

Review of literature data concerning the problem of benign prostatic hyperplasia, comparative characteristics of surgical methods of its treatment; study of risk factors for the development of

late complications and comparative analysis of various methods of their prevention; issues of diagnosis and surgical treatment, as well as methods of drug prevention of postoperative development of urethral strictures and bladder neck sclerosis Assessment of the main risk factors for the development of late complications after open adenectomy and transurethral resection for benign prostatic hyperplasia Evaluation of the effectiveness of a method for preventing obstructive complications after adenectomy and transurethral resection of the prostate by irrigation of the urethra and bladder with a solution of 5-fluorouracil through a modified catheter Analysis of laboratory parameters Analysis of indicators of instrumental examination methods Assessment of the dynamics of the severity of dysuric symptoms in patients after surgery. Assessment of the severity эректильной of erectile dysfunction

1. **Research methods:** Informational and analytical Cross-sectional epidemiological study of the prevalence of late complications of surgery (urethral strictures and sclerosis of the bladder neck) with the calculation of the odds ratio for each of the risk factors Prospective non-randomized clinical study General urinalysis (white blood cells, red blood cells, protein), prostate-specific antigen, creatinine Transabdominal ultrasound examination of the prostate gland with the determination of residual urine volume, uroflowmetry, posterior irrigation urethroscopy, and cystourethrography of the IPSS (International System for Summary Assessment of Prostate Diseases in Points) Scales. ICEF-5 Questionnaire (International Index of Erectile Function)
Research objects

3 **Research objects:** Dissertation research of scientists of the Republic of Kazakhstan, near and far abroad; prelevant articles, theses, reports, monographs presented in the databases of evidence-based medicine (PubMed, Cochrane Library, Google Academy, Scopus, Web of Science, e-library, TripDatabase, ResearchGate); balided questionnaires for assessing the dynamics of the state of health of the Republic of Kazakhstan. assessment of the severity of dysuric symptoms and эректильной the severity of erectile dysfunction. A continuous sample of operated patients in the urology departments of two clinics in Semey. A total of 702 people who were included in the study sample underwent surgical treatment. 246 patients aged 50-80 years living in the Abay region who underwent surgical treatment in the urology departments of the Semey Kidney Center and Semey Emergency Hospital in 2020-2022. The main group of the study included 124 patients who received, in addition to standard postoperative treatment, preventive intervention for five to ten days in the form of washing with a solution of 5-fluorouracil using a modified three-way catheter. The control group consisted of 122 patients combined by age, social status, and place of residence, who also underwent surgery for BPH and received standard treatment. In this group, the bladder was washed with furacilin using a Foley catheter.

For categorical variables, data is presented as absolute and relative numbers. For qualitative data, the significance of differences in groups was determined by calculating the Chi-square criterion (22). For quantitative data, central trends were measured. All quantitative variables were distributed with a deviation from the normal distribution. For quantitative data, given that the distribution was abnormal, the result was presented as the median and 25-75 percentiles. The significance of differences was calculated using the calculation of the Mann-Whitney criterion. Intra-group dynamics were evaluated using the Friedman criterion for K-related samples with repeated measurements. The critical significance level of differences between the groups was assumed to be $p < 0.05$. All statistical analysis procedures were performed using the SPSS 20 program.

The main provisions of the dissertation research submitted for defense:

1. Urethral strictures and bladder neck sclerosis are late obstructive complications of BPH surgery. The main risk factors for their development are the emergency type of hospitalization, infectious inflammation, and the severity of infravesical obstruction prior to surgery. Conservative therapy before surgical treatment has a protective effect against postoperative complications.
2. Irrigation of the bladder and urethra with a solution of 5-fluorouracil through a modified three-way catheter is a new method for preventing the development of urethral strictures and bladder neck sclerosis in the postoperative period.
3. The method of irrigation of the urethra and bladder with a solution of 5-fluorouracil using a modified three-way Foley catheter after surgery in patients with BPH has a high preventive effectiveness against the development of obstructive uropathies and improvement of erectile function.
4. The developed recommendations for the management of patients undergoing surgical treatment for BPH, who have a high risk of developing obstructive postoperative complications, make it possible to identify the patient in the group of high risk of developing late postoperative complications, choose the method of surgical intervention and apply preventive treatment in the early postoperative period.

Conclusions:

1. Urethral strictures and sclerosis of the bladder neck occurred in the postoperative period in 4.9 % of patients. The main risk factors with a statistically significant level were the emergency type of hospitalization ($OR=0.015$, $p=0.006$), the presence of infectious inflammation before surgery ($OR=0.624$, $p=0.042$), and the amount of residual urine before surgery ($OR=1.014$, $p=0.022$). High OR values were also typical for TURP (1.79), overweight and obesity (1.641), diabetes mellitus (1.734), and the duration of the disease for more than a year (2.702). Conservative therapy before surgery had a protective effect, reducing the risk of late complications of surgery by 0.574 times.
2. A method for the prevention of obstructive postoperative complications in the form of irrigation of the bladder and urethra with a solution of 5-fluorouracil through a modified three-way catheter was developed and implemented in practice *трехходовый*.
3. Statistically significant differences in the indicators of leukocyturia and erythrocyturia in the postoperative period were noted in the main group of the study in comparison with the control group. According to the questionnaire using the IPSS scale, 3 и 6 месяцев после хирургических statistically significant differences were found in the main study group and the control group at 3 and 6 months after surgery, indicating the effectiveness of the prevention method and improving the quality of life of patients ($p<0.001$; 0.001, respectively). There was a statistically significant increase in the maximum rate of urination and a decrease in the volume of residual urine in the main group ($p<0.001$; 0.001, respectively). In the control group, nine cases of urethral strictures were registered after six months (7.3%), while in the main group only one patient with infravesical obstruction was identified (0.8%) ($\chi^2=3.855$, $p<0.05$). There was a statistically significant improvement in erectile function in patients of both the main and control groups after surgery for 6 months ($\chi^2 = 115.356$; $p < 0.001$; $\chi^2 = 115.034$; $p < 0.001$, respectively).
4. Based on the determination of the most significant predictors of the development of late obstructive postoperative complications and the results of a clinical study, recommendations for the management of patients undergoing surgical treatment for BPH with high risks of obstructive postoperative complications were developed and implemented in practice *обструктивных*. This algorithm included assessment of the patient's health status at the outpatient stage, identification of the patient as a high-risk group for late postoperative complications, selection of the preferred method of surgical intervention, and use of preventive treatment in the early postoperative period.

Publications: 17 scientific publications have been published on the topic of the dissertation, of which the total number of published articles is only 5, of which 4 articles are in republican peer-reviewed journals approved by the CCSON of the Ministry of Internal Affairs of the Republic of Kazakhstan; 1 article is indexed in the Scopus and Web of Sciencedatabase: "Medicina (Lithuania)", 72 percentile; Total number of published theses in total-3. Certificates of registration in the state register of rights to objects protected by copyright - 2 (No. 42140 of 18.01.2024, No. 43486 of 05.03.2024). Utility model patent No. 4223 dated 09.08.2019. The total number of presentations is 5, including 3 at International conferences in Kazakhstan and 2 at the Republican Scientific and Practical Conference of Young Scientists in Kazakhstan. Certificates of implementation of research results – 2.

Testing of the work:

The main results, methodology, conclusions, conclusions and practical recommendations obtained in the course of the dissertation research were presented at:

Republican scientific and practical conference of Young Scientists "Science and Health" with international participation, dedicated to the memory of Candidate of Medical Sciences, orthopedic traumatologist Молдаханова Amangeldy Moldakhanovich, November 2, 2019, Semey;

XV International Scientific and Practical Conference "Ecology. Radiation. Health", dedicated to the 30th anniversary of the closure of the Semipalatinsk nuclear test site, August 28, 2021, Semey;

I International MED-Congress "Man and Health. Multidisciplinary approach in Medicine" October 18-19, 2022, Semey;

Republican scientific and Practical Conference of Young Scientists with International participation "Modern achievements of young scientists in medical science and healthcare", November 25, 2022, Semey;

International Conference on Emergency Medicine dedicated to the memory of Doctor of Medical Sciences, Professor, Corresponding Member of the National Academy of Natural Sciences of the Republic of Kazakhstan A. Z. Dyusupov, February 23, 2024, Semey.

Scope and structure of the dissertation

The research materials are presented on 111 pages of computer text. The dissertation consists of an introduction, a description of materials and methods, research results, conclusions, practical recommendations, a list of sources used, including 175 references, including 37 domestic and Russian-language, 138 in English, and 5 appendices. The work is illustrated with 23 tables and 20 figures.