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RESEARCH ARTICLE

Predisposing factors for surgical complications in chronic prostatitis and fibrosis of the prostate

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What is not yet known on the issue addressed in the submitted manuscript

The principles of selecting and determining factors of entomology therapy effectiveness for the treatment of NBCP in association with prostate fibrosis.

The research hypothesis

To determine the possibilities and efficacy of entomology therapy for the treatment of bladder outlet obstruction that develops because of prostate fibrosis.

The novelty added by manuscript to the already published scientific literature

Entomology treatment has proven to be a fast, harmless, and promising novelty method of treatment used to correct bladder outlet obstruction, with good clinical results focused on the size of the prostate and significantly decreasing the fibrosis area in the prostate.

Summary

Introduction. Prostatitis is an inflammatory process of the prostate, which continues to be considered one of the most common urological diseases in men under 45. Predisposing factors such as trophic, microcirculatory, and congestive disorders contribute to the onset and development of the inflammatory process in the prostate, as do risk factors such as the urethral catheter, urethrocystoscopy, endoscopic surgery for infection, and deterioration of the integrity of the urethral epithelium. The purpose of this study was to determine the impact of chronic inflammation and fibrosis of the prostate on urodynamics and local prostatic microcirculation and to evaluate the efficacy of conservative treatment.

Material and methods. The study included 58 patients (with pronounced clinical symptoms such as dysuria, stranguria, nocturnal frequent micturition 2-4 times per night, and residual urine greater than 50 mL) who received Adenoprosine[®] 250 mg treatment.

Results. A comparative study of the obtained data was performed on the pre- and post- treatment investigations with Adenoprosine[®] 250 mg suppositories, thus determining the correlation between urodynamic and microcirculation disorders depending on the degree of inflammation and prostate fibrosis.

Conclusion. According to the study results, we can outline that the level of microcirculation and urodynamic impairment indicates the level of prostate fibrosis. This process is reversible in chronic prostatitis with antifibrotic and anti-inflammatory therapy supplemented with Adenoprosine[®] 250 mg.

Keywords: prostatic fibrosis, chronic prostatitis, prostate, Adenoprosine[®] 250 mg.

Introduction

Prostatitis is an inflammatory process of the prostate of unknown etiology, for which methods of diagnosis and treatment have not been sufficiently highlighted [1, 2, 3]. However, prostatitis is still considered one of the most common urological diseases in men under the age of 45 and the third most common urological diagnosis in men over the age of 45, following benign prostatic hyperplasia (BPH) and prostate cancer, and accounting for 14–18% of outpatient visits [2, 4]. According to various literature data, the incidence of prostatitis ranges from 25–35% to 60–80%. The frequency of the disease increases with age, 35% of men under the age of 40 suffer from prostatitis, 45% of men over 40 years old, and 55% of men over 50 years old, etc. [5, 6]. The

early mean age of the patients, the decrease in reproductive function, the persistent disease evolution and treatment approaches, as well as the frequent recurrences, are reasons to consider this pathology both a medical and social problem [7]. The most common pathogens of bacterial prostatitis are the microorganisms of the family Enterobacteriaceae, namely, *E. faecalis*, *P. aeruginosa*, and *P. mirabilis* [1, 7]. However, over the last decade, there has been a marked tendency to involve both atypical microorganisms (*chlamydia*, *mycoplasma*, and *ureaplasma*) as well as staphylococci [8, 9]. The role of anaerobes, gonococci, and *trichomonas* in the development of prostatitis has not been sufficiently studied. The anterior and posterior urethra, as well as other parts of the urinary tract, might be sources of infection. Predisposing factors contribute to the development of inflammatory changes (trophic, microcirculatory, and congestive disorders) within the prostate, whereas the risk factors lead to infection of the prostate gland and damaged bladder epithelial integrity (urethral catheterization, use of urethral plugs, urethral instillation, and urethrocystoscopy). Chronic prostatitis is characterized by less severe clinical symptoms that last for more than 3 months, including perineum pain and discomfort, inguinal pain, difficulty urinating, frequent urination, reduced potency, and poor life quality. However, acute prostatitis differs in its clinical symptoms from the chronic one, being much more pronounced and compelling the patient to visit the urologist immediately.

The pathogenesis of chronic prostatitis has not been definitively highlighted; however, prostate inflammation has been determined to a greater extent due to the pathomorphological studies of surgical or biopsy samples retrieved from benign prostatic hyperplasia or cancer. There is a link between the degree of inflammation and the severity of LUTS (lower urinary tract symptoms) [6]. It has been assumed that the main reason is reduced tissue elasticity due to excessive fibrosis, which is the final stage of a chronic inflammatory process [5, 6]. The development of inflammatory processes involves the physiological healing response due to excessive production of fibrosis and damage or degradation of collagen, unless the inflammation is treated within the acute phase [10, 11]. Collagen is a major component of a large group of extracellular matrix proteins and a subtype that is mostly involved in fiber formation [12, 13]. These, in turn, play an essential role in the formation of the „tissue skeleton“, which provides tissue strength and extensibility, cell migration and adhesion, and tissue regeneration after damage [14, 16]. There are two balanced multidirectional processes of collagen synthesis and degradation, whereas the imbalance results in excessive fibrous (scar) tissue formation that might disrupt the proper function of the target organ [3, 4].

Fibrosis caused by chronic inflammatory disease of the prostate is one of the major complications or causes of subsequent urinary disorders [8, 10], which has been proven experimentally to contribute to its spread on the bladder neck [14]. A retrospective case study in men who underwent surgical intervention for benign prostatic hyperplasia

and prostate cancer showed a significant correlation between the fibrosis degree and malignant prostate tumor development, whereas the tumor was more aggressive in inflammatory processes [10, 13]. It should be noted that prostate fibrosis not only affects the urination process but may also worsen surgical outcomes. The literature data have reported a potential regression of inflammatory consequences due to the enzymatic effect of drugs that might reduce collagen biodegradation and stromal fibrosis by decreasing the process of periglandular and perivascular fibrosis and increasing the vascularization in the prostate [7, 17, 18].

A series of studies has demonstrated the successful use of conservative treatment in acute bacterial prostatitis, leading to regression of inflammatory changes as well as insignificant denaturation of collagen [11, 17, 18]. The early treatment of inflammation in parenchyma of the prostate decrease the risk of early development of fibrosis, however, experimental studies have found that acute inflammation in prostate produce minimal fibrosis, while chronic inflammation, followed by the development of fibrotic changes, leads to a complete recovering of inflammatory process in parenchyma of the prostate [8, 16]. An individual treatment approach for patients with prostate fibrosis is possible due to the emergence and development of ultrasound diagnostic techniques that diagnose the disease, assess the prostatic blood flow, monitor its dynamics, identify the prognosis of blood flow disorders within the impaired prostatic vessels via Doppler ultrasound, and predict possible postoperative complications [3, 7, 18]. A value of quantitative indicators of prostate regional blood flow allows identifying qualitative indicators that may determine the nature of the impaired organ's regional blood flow, such as pulse rate and venous flow velocity, which reveal the venous tone status as well as the presence of pelvic venous disease, including that of the prostate gland [4, 11, 17].

Material and methods

The clinical trial was carried out at Nicolae Testemitanu SUMPh's Department of urology, dialysis, and renal transplantation. The research project and protocol were approved by the Ethics Committee of Nicolae Testemitanu SUMPh. (Minutes No. 6, 11/12/2019). All subjects who participated in the clinical trial signed the informed consent form for participation in the trial.

The purpose of this study was to determine the degree of impact of chronic inflammation and prostate fibrosis on urodynamics and local prostate microcirculation, as well as to identify possibilities for their correction and improvement via drug therapy.

The mandatory diagnostic investigations include laboratory tests that should be carried out in primary health care (complete blood count and urinalysis; the three-glass test (an increase in the number of WBCs in the third portion of urine is characteristic for chronic prostatitis); and a microbiological urine test), as well as instrumental methods, including transrectal ultrasound of the prostate and digital rectal examination. Additional diagnostic assessment in-

cludes serological methods, PCR diagnostic testing (for detection of mycoplasma and chlamydia), uroflowmetry, and prostate biopsy (if necessary).

Blood flow assessment was carried out via transrectal ultrasound dopplerography with General Electric LOGiQP9 equipment, using a sensor at a frequency of 4–10 MHz, which determined the following indicators: maximum systolic blood flow rate, minimum diastolic blood flow rate, resistance and pulsation indices, vein lumen size of the periprostatic venous plexus, and venous blood flow.

Both before and after treatment, a direct relationship to the severity degree of blood flow disorder in the prostate vessels was assessed. Thus, patients with prostate and bladder neck fibrosis exhibited blood flow disorders in the prostatic tissues, which created favorable conditions for complications during different periods of treatment. A retrospective, comparative study was carried out to confirm the correlation between chronic inflammation and prostate fibrosis on urodynamics and microcirculation in the prostate. The study included 58 patients with pronounced clinical symptoms (dysuria, stranguria, 2-4 times nocturnal pollakiuria, post-void residual volume, on average 50 mL), which are characteristic of prostate fibrosis, resulting from chronic prostatitis.

A transrectal ultrasound was initially performed to determine the prostate structure and volume and the presence of prostate fibrosis with or without signs of acute or chronic inflammation. At the same time, patients with benign prostatic hyperplasia or suspected prostate cancer were barred from participating in the study. All patients underwent uroflowmetry, including the assessment of maximum flow rate (Q_{max}), average flow rate (Q_{med}), and speed of urine flow over time. According to the study findings, the patients were divided into two groups. Group I included 26 patients with inflammation and severe fibrosis of prostate tissue, and group II included 32 patients with inflammation and less severe fibrosis, which were graded from 0 (no changes) to 3 points (pronounced changes) based on ultrasound and clinical data.

Subsequently, all patients were given a course of treatment with Adenoprosine® 250 mg (as suppositories) for three weeks. The complaints decreased in 21 patients at the end of treatment, and they ceased. These patients – 6 (23.1%) from the group with severe inflammation and fibrosis and 15 (46.9%) from the group with inflammation and initial fibrosis – were recommended for dynamic outpatient care visits to the urologist. Despite an improvement in the condition of the other 37 patients, characterized by reduced complaints and better clinical and paraclinical parameters, it was recommended that they continue administering conservative Adenoprosine® suppositories for 30 days more, followed by subsequent follow-up investigations. Three patients from the study (2 from group I and 1 from group II, respectively) underwent endoscopic bipolar transurethral incision of the bladder neck and prostate (TURP) under spinal anesthesia, followed by the retrieval of biopsy material for pathomorphological examination.

Results and discussions

A comparative study of the obtained data was performed on the pre- and post-treatment investigations with Adenoprosine® 250 mg suppositories, thus determining the correlation between urodynamic and microcirculation disorders depending on the degree of inflammation and prostate fibrosis.

The fibrosis degree in patients from group I (with severe prostate fibrosis) decreased insignificantly by 0.1 points compared to 0.4 points in the group with milder fibrosis. The degree of inflammation was significantly lower in both groups, namely, 0.8 and 1.0 points, respectively, which proves the effectiveness of anti-inflammatory treatment with Adenoprosine® 250 mg suppositories. These very results were confirmed by the pathomorphological assessment (in three patients), characterized by a more reduced fibrous tissue area in patients from group II and a lack of acute inflammatory areas in the histological samples from both groups. All 37 patients from both groups exhibited an improvement in the maximum and average flow rates at the end of treatment and an insignificant decrease in prostate volume, resulting from a reduced inflammatory process in the prostate following treatment with Adenoprosine®.

According to ultrasound findings, all 37 patients undergoing an additional treatment approach showed some structural changes of the prostate, including inhomogeneous echogenic tissue and increased and decreased foci of echo density. Patients from group I had only a 0.1-point decrease in the degree of fibrosis, whereas the degree of inflammation decreased by 0.8 points. The second group showed more significant alterations in fibrosis and inflammation degree, viz. 0.4 and 1.0 points, respectively. Q_{max} increased by 1.5 mL/s and Q_{med} by only 0.5 mL/s in patients from the first group with severe prostate fibrosis. The second group (patients with minimal prostate fibrosis) had significantly better uroflowmetry values, viz. 3.9–4.0 and 4 mL/s, respectively. Microcirculatory disorders were also more pronounced in patients from group I compared to those with moderate fibrotic changes from group II. The indices of microcirculatory disorders were three times higher in group I compared to group II. Prior to treatment, 17 (46.0%) patients out of the 37 patients exhibited vein dilation of the periprostatic venous plexus up to 3.5±0.6 mm and a blood flow rate of up to 6.2±1.3 cm/s. The post-treatment indices showed a reduced vein dilation of the periprostatic venous plexus up to 2.5±0.2 mm in 9 (24.3%) patients and a better blood flow rate up to 9.1±0.3 cm/s. Table 1 shows a comparison of data analysis in patients before and after treatment.

Ultrasound investigations with the transrectal sensor recorded an irrelevant decrease in the mean volume of the prostate due to reduced prostate edema and a decreased inflammatory process. The pathomorphological study of a biopsy sample obtained via endoscopy in 3 patients confirmed stromal fibrosis with elements of paravascular fibrosis, which was more severe in two patients from group I.

Table 1. The investigation findings in both groups of patients, depending on the degree of fibrosis and inflammation before and after therapy with Adenoprosine® 250 mg, suppositories (37 patients).

Groups Qmax mL/s		Indices					
		Qmed mL/s	Degree of fibrosis	Degree of inflammation	Fibrosis stage (ultrasound-based)	Prostate volume, cm ³	
Group I (20 patients)	Before therapy	10.8±2.5	6.3±0.4	2.5±0.2	2.6±0.25	Advanced > 70%	36±0.2
	After therapy	12.3±2.3*	6.8±0.1***	2.4±0.1**	1.8±2.3**	> 60%	35.5±0.03*
Group II (17 patients)	Before therapy	15.6±1.2	9.4±1.5	0.6±0.01	2.2±0.15	Moderate 50-70%	37.6±0.52
	After therapy	19.5±1.5**	13.4±1.5*	0.2±0.15*	0.2±0.13*	> 30%	36.4±0.01**

Note: statistically significant values after treatment compared to initial ones: * - $p < 0.05$; ** - $p < 0.01$; *** - $p < 0.001$; Qmax – maximum flow rate; Qmed – medium flow rate.

Therefore, it has been found that chronic inflammation associated with fibrosis might exacerbate the local microcirculation and the urodynamics. Chronic prostatitis, complicated by advanced fibrosis tissue, causes significant, irreversible damage to the prostate parenchyma and local blood flow. However, moderate impairment of the prostate parenchyma is likely to partially restore and improve the urodynamics and microcirculation. Thus, the conservative treatment with Adenoprosine® 250 mg suppositories used to prevent fibrosis formation and regression has a good pathogenetic rationale.

Conclusion

In conclusion, the study results proved that the impaired microcirculation and urodynamics indirectly indicate the stage of prostate fibrosis. In chronic prostatitis, this process is reversible if anti-fibrotic and anti-inflammatory drugs are administered, supplemented with Adenoprosine® 250 mg suppositories.

Declaration of conflicting interests

The author declares the absence of any conflict of interest in the elaboration of this article.

Authors' contribution

Both authors contributed equally to the development of the manuscript and approved its final version.

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