ORIGINAL PAPER

Echoguided drug infiltration in chronic prostatitis: results of a multi-centre study.

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Summary

Objectives: In chronic prostatitis there are many causes that may provoke a therapeutical failure of a systemic antibiotic treatment. At the moment a consensus has not been reached on the efficacy of the many therapeutical options that are available with not one of these approaches being efficacious in all patients. In our view the main causes of treatment failure are the well-known hurdle to antibiotic diffusion inside the glandular parenchyma associated with the so-called intraprostatic bacterial biofilms and the possible presence of local auto-immune reactions. Given this background we tested ultrasound guided intra-prostate infiltration of a cocktail of antibiotics and betamethazone, for a therapeutical options. Material and Methods: 320 patients, referred to us because of symptoms indicative of chronic prostatitis, were enrolled in this study. The inclusion criteria were the severity of the symptoms and the failure of repeated cycles of antibiotics in the previous 12 months. At the initial consultation patients completed the NIH Prostatitis Symptoms Index (NIH-CPSI). All underwent: a) Digital rectal examination (DRE), b) Transrectal prostatic ultrasound scan (TRUS), c) Uroflowmetry, d) Cultures of first voiding and after prostatic massage urine and cultures of sperm for saprophytic and pathogen germs, yeasts and protozoa, e) DNA amplification with Polymerase Chain Reaction (PCR) on urine and sperm, for Chlamydia Trachomatis, Mycoplasmata (Ureaplasma Urealyticum and Mycoplasma hominis), Gonococcus, HPV and HCV. Patients on the basis of laboratory results received a cocktail of antibiotics associated with Betamethazone. The cocktail was administered as prostate infiltration. Administration was repeated after 7 and 14 days. Final assessment of the efficacy of therapy included not only the NIH-CPSI scores but also the patient's subjective judgement expressed as a "percentage overall improvement". The percentage judgements were arbitrarily divided into 4 classes: 0-30 no improvement % (Class I); 30-50% satisfactory improvement (Class II); 50-80% good improvement (Class III; 80-100% cured (Class IV). Results: Statistical analysis of the results showed that 68% of patients were included in the Class IV and 13% were no responders (Class I). Conclusions: In our opinion this is one of the more valid therapeutical approaches to chronic bacterial or abacterial prostatitis also if it requires more studies.

KEY WORDS: Prostatitis; Drug prostatic infiltration; Chronic pelvic pain syndrome; Autoimmunity, Cytokines.

INTRODUCTION

Many urologists loathe to deal with chronic prostatitis even though it is one of the most common and invalidating pathologies of the male uro-genital system. Although the incidence is not as high as the 30-50% Drach and Barbalias originally estimated, prostatitis is still very frequent. 5-10% of the male population is affected, according to European estimates and about 8-9% according to the National Ambulatory Medical Care Survey (1-3). Despite these figures, a consensus has not been reached on the efficacy of the many therapeutical options that are available (Antibiotics, Alpha blockers, Finasteride, Pentosan polysulphate, Saw palmetto,

Table 1.

Perugia Urology Department Symptoms Index (PUD-PSI).

Voiding symptoms	0	1	2	3
During the night I pass water	never	once	twice	more
During the day I pass water	> 3 hours	> 2 hours	< 2 hours	more often
My urinary flow is	strong	impaired	thread-like	***
Flow properties	normal	abnormal	***	***
Dripping	absent	sometimes	always	***
Pain Symptoms	0	1	2	
Micturition burning	absent	moderate	severe	***
Perineal soreness	absent	moderate	severe	***
Inguinal soreness	absent	moderate	severe	***
Scrotal soreness	absent	moderate	severe	***
Coccygeal soreness	absent	moderate	severe	***
Suprapubic soreness	absent	moderate	severe	***
Ano-rectal soreness	absent	moderate	severe	***
Sexual Symptoms	0	1	2	3
Sexual desire	normal	25% lost	50% lost	absent
Erection	normal	25% lost	50% lost	absent
Ejaculation time	normal	25% less	50% less	premature
Ejaculation properties	normal	hampered	painful	absent
Sperm aspect	normal	insufficient	agglutinated	bloody
Ejaculation jet energy	normal	decreased	dripping	***

ProstaQ, Surgery, etc) with not one of these approaches being efficacious in all patients (2, 4-6).

In our view the main causes of treatment failure are multiples. On the one hand the well-known hurdle to antibiotic diffusion inside the glandular parenchyma associated with the so-called intraprostatic bacterial biofilms and on the other the possible presence of local auto-immune reactions. The bacterials biofilms encapsulate the infected areas and act as a barrier against antibiotics and the immune defence system. The autoimmune reaction releases cytotoxic substances and pro-inflammatory agents and create a vicious circle of infection and inflammation (4, 7-10). The microfilm hypothesis was developed by Nickel in 1994 (4) and later confirmed by direct microscopy observations (7, 8). Bacterial microfilms are caused by the adhesin-mediated sticking of plancton microorganisms to a tubular surface such as the walls of a prostatic duct. Microorganisms adhere in groups of 10-12 cells to form adjacent encapsulated micro-colonies which conglomerate and create the mature biofilm. In vitro studies have shown that antibiotics' concentration needs to be over 100 times the normal MIC in such conditions. Rupture of the biofilms releases the germs and the required antibiotic dosage drops to normal levels. Consequently biofilms formation creates a vicious circle of pathogen survival and proliferation despite treatment with antibiotics; the bacterials' agglomerates within the ducts obstruct the lumen and facilitate accumulation of infected glandular secretions. The micro-organisms produce a exopolysaccharide slime which, besides providing a habitat for their hibernation, also strongly stimulates a damaging immune response causing chronic inflammation of the prostatic parenchyma.

The possible cascade of events is as follows:

- Acute bacterial or abacterial infection (Chlamydia, Mycoplasmata etc) starts.
- The prostate parenchyma is invaded and microbial mucopolysaccharide biofilms form within the prostate ducts and sequester the infectious agents.
- Prostatitis becomes chronic.
- Autoimmune process may starts, maybe in the presence of a congenital genotype with low Interleukine-10 production (Shoskes 11) causing tissue auto-reactivity.
- Chronic inflammation is by now independent of the original infection and can no longer be treated with standard therapy.

Hence the need for a different approach. In this study we describe the effects of an innovative intraprostatic infiltration of antibiotics and cortisone, that was designed to overcome the encapsulating barrier and to limit or inhibit local auto-immune reactions.

Materials and Methods

320 patients with symptoms of chronic prostatitis were enrolled in this study between 1999 and 2002. The study is been submitted to the Ethical Committee of each participant Centre. The inclusion criteria were failure of repeated cycles of antibiotics in the previous 12 months and the severity of the symptoms with a NIH-CPSI ≥ 21. Each patient signed an informed consent and provided a case history, the NIH Chronic Prostatitis

Table 2.

*Percentageof pathogens in urine before and after therapy (*asDNA and Iga).*

	Baseline	3 Months	6 Months	12 Months
Enterococcus sp	10%	0%	1.3%	4%
Escherichia Coli	12%	1.8%	2%	2.8%
Klebsiella	3.5%	0%	2.2%	1.5%
Staphilococcus	9%	0%	2.1%	3.1%
Streptococcus	1.2%	0%	1.1%	0%
Others	0%	1.0%	0%	0%
Yeast	0%	0%	0%	0%
Chiamydia*	4%	0%	1.3%	1.3%
Gonococcus	1.7%	0.8%	0%	0%
HPV	8.8%	5.8%	7.0%	5.6%
Micopiasmata	3.5%	0%	0%	0%

Symptoms Index Questionnaire (NIH-CPSI) and the Perugia Urology Department Prostatitis Symptoms Index (PUD-PSI) (Table 1) (12). All underwent: a) Digital rectal examination (DRE), b) Transrectal prostatic ultrasound scan (TRUS), c) Uroflowmetry, d) Cultures of first voiding and after prostatic massage urine and cultures of sperm for saprophytic and pathogen germs, yeasts and protozoa, e) DNA amplification with Polymerase Chain Reaction (PCR-DNA) on urine and sperm, for Chlamydia Trachomatis, Mycoplasmata (Ureaplasma Urealyticum and Mycoplasma hominis), Gonococcus, HPV and HCV.

DNA was extracted according to the phenol-chloroform procedure (Sambrook et al. (21). The PCR reaction was performed in a total volume of 50 ml containing 5 ml of 10X PCR Buffer II (500 mM KCl, 100 mM Tris HCl, pH 8.3 - Applied Biosystems), 1.5 mM $MgCl_2$, 200 mM of each dNTP (Roche Diagnostic, Italy), 2.5 IU AmpliTaq Gold Polymerase (Applied Biosystems), 10 pmol of each primer. The cycling condition used was 35 cycles of 30 sec at 94°C, 1 min at 55°C, 1 min at 72°C. Each round of PCR was preceded by an initial 10 min denaturation step at 95°C (to activate AmpliTaq Gold) and followed by a final extension step of 10 min at 72°C. A nested PCR approach was used to amplify Neisseria gonorrhoeae. All the reactions were cycled on a GeneAmp® PCR System 9700 (Applied Biosystems, USA). For monitoring PCR amplification, 5 ml of each PCR product was subjected to electrophoresis for 5 min at 150V on 2% agarose gel in 1X Tris-Borate/EDTA buffer stained with 0.5 mg/ml ethidium bromide.

Each patient received an intraprostatic infiltration of Desametazone 12 mg combined with Rifampicyn 300 mg and Levofloxacine 25 mg. In presence of Gonococcus we replaced Levofloxacin with Ceftriaxone 1 g in presence of yeasts we add Fluconazole 6 mg and in presence of protozoa we add Methronidazole 15 mg. The antibiotic cocktail was administered by transperineal echoguided intraprostatic infiltration either in a random way or inside in any fibrous areas with the aim to sterilize them. We used Toshiba PowerVision 6000 ultrasound scanner with transrectal biplanar multifrequency (6-10 MHz) probe equipped with angiodoppler. The injection needle was Echojet® 23 gauge, 200 mm in length. The needle was inserted 1 cm to the left or the right of the median raphe, according to the site of inflammation, and 1 to 3 cm above the anal sphincter, this point corresponding to the projection of the prostate apex. After the needle had been inserted into the subcutaneous layer, 2 cc local boluses of lidocaine were administered again and again as the needle was pushed towards the apex of the prostate. Attention was focused on anaesthetizing the urogenital diaphragm and the prostatic capsule. A complete treatment included three infiltrations, performed the 1st, the 10th and the 20th day.

Follow-up

Six and twelve months after the last infiltration, all patients underwent uroflowmetry, all microbiological testing, the NIH-CPSI and the PUD-PSI. For an overall evaluation of therapy, each patient was asked to provide a subjective assessment of treatment by quantifying the improvement on a scale of 0-100. The results of this last evaluation were divided into 4 classes: 0-30% “so called” non-responders (Class I); 31-50% moderate improvement (Class II); 51-80% good improvement (Class III); 81-100% marked improvement/cured (Class IV).

Statistical Analysis:

The Friedman test for related data was applied at the basal time, 6 and 12 month check-ups to the uroflowmetry results, the bacteriological examinations, the NIH-CPSI and the PUD-PSI.

RESULTS

The mean age of patients was 38 years (range: 21-54 years) and the mean time since disease onset was 5.3 years (range: 6 months - 22 years). The percentage of pathogens detected in the sperm and urine by cultures and PCR-DNA before and after therapy are reported in Tables 2 and 3.

In the follow-up of overall patients, not statistical significant differences emerged in uroflowmetry results and in the PUD-PSI regarding voiding and sexual symptoms.

Table 3.

*Percentage of pathogens in sperm before and after therapy (*as DNA and Iga).*

	Baseline	3 Months	6 Months	12 Months
Enterococcus sp	38.3%	2.5%	0%	3.7%
Escherichia Coli	14.2%	0.7%	0%	0%
Klebsiella	5.8%	0%	2.4%	5.2%
Staphilococcus	12.9%	9.9%	5.5%	5.5%
Streptococcus	3.9%	3.0%	1.1%	0%
Others	7.7%	1.0%	0%	0.5%
Yeast	0.2%	0%	0.4%	0.3%
Chlamydia*	36.3%	12.7%	5.0%	3.3%
Gonococcus	17.5%	3.2%	0%	0%
HPV	14.9%	7.5%	8.2%	4.4%
Micoplasmata	4.5%	6.4%	4.0%	2.0%

Significant differences were observed in the NIH-CPSI ($p<0.01$) and in the PUD-PSI regarding pain symptoms ($p<0.01$) (Table 4).

The subjective improvement evaluated by each patient demonstrated that 218 patients (68%) were marked improved or cured (Class IV), 15 patients (5%) were improved as good (Class III), 45 patients (14%) as moderate (Class II), while 42 patients (13%) fell into the class of so-called non-responders (Class I). This last class included a sub-group of 29 patients who did not respond at all. The patients of Class IV showed a significant improvement at six and twelve months regarding NIH-CPSI ($p<0.001$), PUD-PSI voiding ($p<0.01$), pain ($p<0.001$) and sexual symptoms ($p<0.01$).

Side effects of treatment:

a) Immediate: Pain during infiltrations was very rare. Somebody referred a mild burning sensation at the tip of the penis. 11% of patients complained of a drop of blood in the first 2 or 3 micturitions following an accidental perforation of the urethra (0.5% of cases). No therapy was required.

b) Delayed: Haemospermia in 81% of patients was observed usually at the first post-infiltration ejaculation and 2% required coagulant treatment (tranexamic acid orally). Transient worsening of prostatitis symptoms occurred in 13% of patients, usually on the 2nd day after infiltration and disappeared within 24-36 hours. Nimesulide, as pain-killing was prescribed in these cases and symptoms were resolved quickly. Intra-prostatic hematoma developed in 8 patients (3%) and was associated with perineal soreness for 48-72 hours and blood in the ejaculate for up to 15 days. It resolved spontaneously in 7 cases while 8 required ultrasound guided removal of the collection without any further complications.

c) Persistent: Only one patient, two years after a single infiltration, complains of abnormal penile sensitivity and erectile disturbances even though NTP Rigiscan and penile Echo-Doppler are normal.

Discussion

The many theories on the pathogenesis of chronic prostatitis are not necessarily mutually exclusive. Acute urethral infection may rise to the prostate and become chronic because of insufficient therapy or an inadequate immune defense system (13). A sterile uretro-prostatic reflux with intra-parenchymal precipitation of urates may trigger chronic inflammation as may local autoimmune reactions (9).

Repeated courses of antibiotics are undoubtedly helpful, particularly in cases of bacterial prostatitis and most urologists agree that even the so-called abacterial forms of prostatitis benefit from prolonged antibiotic treatments (14). To reach a therapeutic concentration in prostatic tissue the ideal antibiotic needs to be liposoluble, with a low grade of plasma ionization (pKa),

Table 4.

*Follow-up results. *Friedman test for related data.*

	Baseline	3 Months	6 Months	12 Months
Uroflowmetry (F.max)	19.6±3	21.7±3	21.5±2.7	NS
NIH-PSS	25±5	20±3	17±3	<0.01
PUD-PSI (voiding)	3±1	2.5±1	2.5±1.5	NS
PUD-PSI (pain)	4±0.5	3-2±1	3±0.5	<0.01
PUD-PSI (sexual)	4±1	3.1±0.5	3±0.5	NS

an acid pH and poor protein binding properties. However, treatment with even these agents often fails apparently because of impenetrable bacterial biofilms within the prostate and serious local auto-immune reactions (9, 10).

For all these reasons we opted for a cocktail of antibiotics and cortisone. The etiology of prostatitis justifies the use of antibiotics as the resistance of chronic prostatitis is due not only to the difficulty in diffusing the drugs within the prostate but also to the presence of the encapsulating bacterial biofilms. Besides in our previous trial (15) we have doubted, the real existence of abacterial prostatitis. Desametazone was associated in an attempt to break up the vicious circle of immune reactions and inflammation which is intrinsically linked to the disease. Several other reasons underlie the decision to infiltrate antibiotics with cortisone into the prostate. When drugs are injected directly into the prostate they reach local concentrations that are about 2,000-2,500 times higher than with systemic administration and they can overcome, if present, the perimicrobial polysaccharide barrier of the biofilms. The quinolonics and the macrolides inhibit Cytokine release, particularly IL 2, IL 6 and TNF (16), which coincidentally are the same cytokines that are found in high concentration in the semen and EPS of men with prostatitis (Shoskes et al., 11). Furthermore, cortisone not only inhibits possible allergic reactions to antibiotics, which were not, by the way, observed in any of our patients, but also inhibits Cytokine release. Conversely, high antibiotic concentrations counteract the hypothetical risk of steroid-induced intra-prostate abscess or weakening of the host defence system.

This study may be criticized on its lack of a control group which, for obvious ethical reasons, could not be recruited as the invasive nature of the infiltration precluded its use to administer placebo. Moreover, in study without a placebo group it is important to establish that the treatment given did actually cause improvement. This question can be answered by comparing for each patient the incidence and the improving of symptoms before and after the treatment. Besides these patients acted as a control group for themselves as they had already undergone several unsuccessful cycles of systemic antibiotic therapy before being recruited to this study. Another limitation is our use of a subjective assessment of efficacy as the overall percentage of improvement. However, in our experience, the assessment of the overall efficacy of therapy could not be evaluated simply in terms of negative bacteriological results, even though the difference between the pre and post infiltrations tests was significant, or evaluated in a reduction in the symptom scores, because chronic prostatitis has a marked psychological and behavioral impact. In fact, the disappearance or the improvement of some symptoms is not always associated with the patient's awareness of recovery and vice versa.

Conclusions

Over the years the results of intra-prostate infiltration of antibiotics have been, on the whole, disappointing. The reasons for the success of our approach appear to be in a depth bacteriological analysis, aimed at detecting Chlamydia and Gonococcus and in the use of a high definition ultrasound probe (7-10 MHz) to visualize and infiltrate areas of inflammation and fibrosis. The fibrotic areas definitively must be infiltrated in order to make them "explode", which is the only way to ensure they are sterilized.

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