

Results of Treatment with Pollen Extract (Cernilton ®) in Prostatodynia and Chronic Prostatitis

E. W. Rugendorff, W. Weidner, L. Ebeling, A. C. Buck

Introduction

The results of treatment in patients with symptoms of chronic prostatitis are often disappointing. This is partly due to controversy regarding the etiology and clinical significance of the different forms of the benign painful prostate (18), and in particular, a failure to use the diagnostic criteria and methods necessary for the differential diagnosis of the various forms of prostatic disease. However, even if a precise classification in chronic bacterial or non-bacterial prostatitis and prostatodynia has been reached, there is no treatment which will guarantee a lasting cure and many patients suffer for years or even decades from persisting symptoms (38).

Clinical investigations with a defined pollen extract (Cernilton ®**, A. B. Cernelle, Sweden) have provided evidence of symptomatic improvement in benign forms of prostatic disease (4,5,13,14,19). Here we report the results of a prospective study carried out in 90 patients to investigate the efficacy of Cernilton ® in respect to voiding dysfunction and inflammation in chronic prostatitis syndromes.

Patients and Methods

There were ninety patients, 19 to 90 years of age (median 45, mean $47.2 \pm SD 17.6$), with symptoms of prostatitis of at least one-year duration and no positive cultures localizing a bacterial pathogen to the prostate included in this case control study (trial center E. W. R.). Of these 90 patients 30 had a history of bacterial prostatitis and at least two previous episodes of confirmed urinary tract infection, but entered into the study in the infectionfree interval after anti-bacterial treatment. Patients with urinary tract infection, anogenital syndrome, or benign prostatic hyperplasia influencing the clinical conditions, and patients with concomitant therapy with muscle relaxants, alpha-adrenergic blockers, or diuretics were not included in this study.

The differential diagnostic investigation was based upon bacterial localization cultures from urine samples and expressed prostatic secretions (EPS) by the technique recommended by Meares and Stamey (32). Additionally, leucocyte counts in the first-voided 10ml of urine (VB 1), mid-stream urine (VB 2) and first-voided 10ml urine after prostatic massage (VB 3) were analyzed. Using the sediments in these different urine specimens the leucocyte count was performed with a counting chamber (MD-KovaSysteme) (40) calculating the number of leucocytes in VB 3 per μl .

Additional investigations (ultrasonography, voiding and/or retrograde cystourethrography, endoscopy) revealed complicating factors (CF) in 18 patients. The complicating factors were bladder neck sclerosis in ten, urethral strictures in five, and excessive prostatic calcifications in three cases. Eight patients had undergone a previous transurethral or open prostatectomy, seven for benign prostatic hyperplasia and one for chronic prostatitis.

There were 44 patients (48.9 %) who had received treatment with various drugs (antibiotics, anti-inflammatory agents, urological remedies, etc.) during the three-month period before commencement of the study; 37 of them had noted some, but unsatisfactory, improvement.

Treatment with Cernilton ® was given in a dosage of one tablet 3 times daily and in most cases continued for a period of six months.

The following parameters were recorded before treatment and after 3 months and 6 months of therapy: (i) symptoms [discomfort and pain scored in: absence of the symptom or in mild, moderate and severe intensity of the symptom; nocturia, frequency, and dysuria, scored according to Bojarsky et al. (10)1; (ii) findings on rectal palpation of the prostate (normal or enlarged prostate; normal, smooth, increased, or irregular consistency of the prostate); (iii) uroflow (voided volume, flow time, micturition time, mean flow rate, time to peak flow, peak flow rate); (iv) leucocyturia in VB 2 and VB 3; (v) bacteriuria; (vi) complement C3 and coeruloplasmin in the ejaculate [scored semiquantitatively, combining the values of complement C3/

coeruloplasmin per dl according to a modified scheme of Bloik and Hofstetter (8) as follows: 1 = < 1,5 mg / negative; 2 = 1,5 - < 2 mg / <0,5mg; 3=2-4mg/0,5mg-1mg; 4=3-8 mg/ 1-3mg].

Complement C3 and coeruloplasmin were determined in the ejaculate after liquefaction, centrifuged for five minutes at 11,266 U /min resp. at 10,500 g. The radial immunodiffusion of the supernatant sample was performed with LC-Partigen®-C3c and LC-Partigen® plates (Behringwerke AG, Marburg, Germany). In addition to the sample, a control from a calibrated standard serum was filled on the plates (dilution 1:20 for complement C3; dilution 1:11 for coeruloplasmin). The amount of complement C3 and coeruloplasmin was calculated from the diameter of the sample precipitate according to the calibration curve from calibrated standard serum of complement C3 and coeruloplasmin (Behringwerke AG, Marburg, Germany).

When assessing the therapeutic results, a complete response with normalization of all parameters was defined as "cure" an improvement in the parameters as "improvement," and persistence or deterioration of the parameters as "no improvement."

The biometrical evaluation was performed by descriptive analysis of the parameters before and after treatment, also in relation to the changes after 6 months of treatment as compared with the status after 3 months of treatment. The following tests were used: (i) the t-test for related samples for the comparison of the uroflow parameters; (ii) the Wilcoxon matched-pairs signed-ranks test using chi2 approximation for the comparison of the leucocytes in VB 3; (iii) the sign test for the scored complement C3 / coeruloplasmin in the ejaculate; (iv) the Pawlik corrected contingency coefficient for qualitative, and the Spearman rank correlation coefficient for quantitative correspondence between the changes of leucocyturia in VB 3 and the peak urine flow rate.

Results

The clinical status at baseline is characterized mainly by mild to moderate symptoms. The prostate was enlarged in 55.6 % and tender in 94.4 % of the patients. Complement C3 in the ejaculate was above 1.5mg/dl in all cases. Due to significant differences of the parameters at baseline and in their courses the results of the treatment in patients without (N = 72) and with (N = 18) complicating factors [CF] are described separately.

Symptoms

Almost all of the patients complained of frequency of voiding and dysuria, while pain was present in about two-thirds. Patients with associated CF responded poorly, whereas in cases without CF the symptoms were reduced markedly after six months of treatment (Table 1).

Palpation of the prostate

In patients without CF the initially enlarged prostate returned to a normal size in 15 / 39 cases, the consistency of the prostate improved in 37 / 68 cases, and the prostate was no longer tender on palpation in 47 / 71 cases after treatment. The consistency and the tenderness worsened in five patients. The findings on palpation in the group with CF showed practically no change or deterioration.

Uroflow

In contrast to the patients with CF, where all the uroflow parameters worsened, there was a definite improvement ($p < 0.05$) of the time to peak flow by increased voided volume in the cases without CF. Micturition and flow time remained unchanged. The peak urine flow rate (PUFR, ml/s) showed a slight decrease from 11.9 ± 3.9 to 10.5 ± 2.6 ($-x \pm SD$) in patients with CF. The mean urine flow rate (ml/s) in patients without CF increased from 7.4 ± 2.7 ($x \pm SD$) to 9.1 ± 3.4 ($x \pm SD$) after three ($p < 0.001$) and to 10.8 ± 4.5 ($-x \pm SD$) after six months of therapy ($p < 0.001$; also comparing six vs. three months). The PUFR at baseline was 15.9 ± 5.2 ($x \pm SD$) in cases without CF and increased to 19.0 ± 7.2 ($x \pm SID$) and 23.9 ± 10.6 ($x \pm SD$) respectively, at the control after three ($p < 0.001$) and six months of treatment, respectively ($p < 0.001$; also comparing six vs. three months).

Tab. 1 Symptom response to treatment in patients without complicating factors (N = 72)

Symptom	free	improved	N
Discomfort	67.9%	9.4%	53
Pain	69.4%	12.2%	49
Nocturia	55.5%	29.6%	54
Frequency	48.6%	26.4%	72
Dysuria	52.2%	11.6%	69

* Details: see "Patients and Methods".

Leucocyturia in VB 3 (L-VB 3)

In patients with CF, the L-VB 3 increased in the median from 80 to 185 leucocytes / μ l ($p < 0.001$). Comparing the number of leucocytes before and after treatment in patients without CF, the L-VB 3 decreased in the median from 50 to 20 leucocytes / μ l ($p < 0.001$). The mean ($x \pm$ SID) from 85.9 ± 89.9 at baseline decreased to 69.1 ± 121.8 at the three-month ($p < 0.001$) and to 42.2 ± 62.6 at the six-month control ($p < 0.001$; also comparing six vs. three months). Figure 1 shows the individual changes, which are documented separately as pre-post-values according to different levels (< 50 , $50 - 99$, $100 - 1000$ leucocytes / μ l) of baseline values.

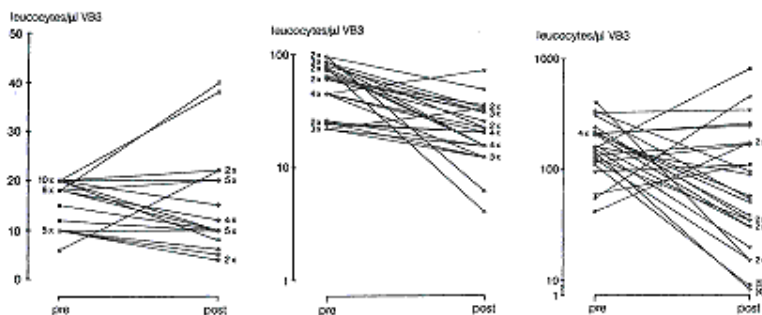


Fig. 1 Individual courses of the leucocyturia in VB 3 in patients without complicating factors (N = 72), separately plotted according to different baseline (pre: < 50 , $50-99$, $100-1000$ leucocytes/ μ) or control (post) values. In brackets=two values of numbers of leucocytes (control). (Details: see "patients and Methods.")

L-VB 3 and PUF_R

Comparing the changes of the L-VB 3 and the PUF_R in patients without CF, the L-VB 3 decreased in three cases with a decreased PUF_R and in 52 cases with an increased PUF_R. An increase of the L-VB 3 was observed in eight cases with a decreased PUF_R and in nine cases with an increased PUF_R.

The inverse qualitative changes of the L-VB 3 and the PUF_R were highly correlated ($CC_{co} = 0.720$). This correlation is confirmed by the inverse correspondence ($r_s = 0.565$) between the quantitative changes of the L-VB 3 and the PUF_R. Because of the extremely widespread pattern in the distribution of the leucocyte numbers in VB 3, the individual differences between the baseline value and the control value after treatment were separately ranked for L-VB 3 and PUF_R according to the definition of rank 1 as strongest decrease and of rank 90 as strongest increase, and plotted as combined ranks of the individual changes for both parameters (Fig. 2).

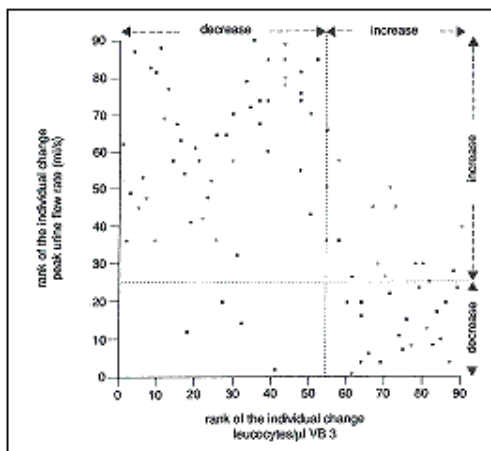


Fig. 2 Scattergram of the combined ranked individual changes of the leucocyturia in VB 3 (L-VB 3) and the peak urine flow rate (PUFR) in patients with chronic prostatitis syndromes (N = 90) comparing the values before and after treatment. High inverse qualitative ($CC_{corr} = 0.720$) and quantitative ($r_s = 0.565$) correlation between the changes of L-VB 3 and PUF_R. Rank 1 =strongest decrease, rank 90 =strongest increase, parallel lines to ordinates =no change (conversion point). (Details: see "Patients and Methods.")

Complement C3/coeruloplasmin

In correspondence with the changes of the L-VB 3, patients without CF showed a decrease of the inflammation parameters complement C3/coeruloplasmin in ejaculate after three ($p < 0.001$) and a further reduction after six months of treatment ($p < 0.001$; $p = 0.005$ comparing six vs. three months), whereas an increase was documented in cases with CF ($p = 0.07$) (Table 2).

Assessment of Efficacy

As therapeutic result in the cases without CF, 56 out of 72 patients (78 %) responded: 26 patients (36 %) were cured and 30 patients (42 %) were improved. In 16 cases (22 %) no improvement or deterioration was registered. In patients with CF, only one responded (6 %) with improvement. The remaining 17 patients (94 %) did not improve or deteriorate.

Discontinuation of Treatment

Treatment was discontinued because of clinical deterioration or ineffective response in 12 patients. The most frequent cause of deterioration was symptomatic bacteriuria (83.3 %) to be treated with anti-bacterial therapy. CF were present in 66.7 % of all patients in whom treatment was discontinued.

Tolerance

In 96.7 % of the patients the pollen extract showed a good tolerance. Unwanted events were registered as meteorism, heartburn, or nausea in three patients. These transient gastrointestinal symptoms were mild to moderate and did not require discontinuation of treatment.

Discussion

The chronic forms of bacterial prostatitis often relapse after therapy (17,22,38). Independent of the fact that new antibacterials such as fluoroquinolones show a good antibacterial efficacy (1,15,39,49), in the infection-free interval there are still many patients presenting prostatitic symptoms and signs despite negative urine and expressed prostatic secretion cultures.

In the so-called non-bacterial prostatitis three forms can be distinguished: patients with "Ureaplasma-associated" prostatitis, or with evidence of Chlamydia trachomatis infection, or without pathogens detectable in the EPS and/or in VB 3 (47). Although the possible etiological role of Ureaplasma and Chlamydia trachomatis remains controversial, and in spite of the culture problems due to contamination (20), there is increasing evidence of their role as pathogens (12,16,24,27, 29,34,35,48). However, anti-bacterial treatment is necessary in the case of a clearly established pathogen, but mostly, the EPS and the VB 3 are sterile.

A common observation in the condition defined as prostatodynia is the presence of reduced PUFRR and increased maximum urethral closure pressure (MUCP) suggesting the use of relaxants and alpha-adrenergic blocking agents (3,7,31,36,37,46). The persistence of symptoms in these patients has even been ascribed to a psychosomatic element (11,41,43).

Thus, summarizing the therapeutic outcome in patients with chronic prostatitis syndromes, there is a need for conservative management which leads to symptomatic relief, to an improvement of the voiding disturbance, and to a reduction or even elimination of the inflammation in the prostate.

In this study the pollen extract, Cemilton®, was found to be effective in the treatment of prostatodynia and chronic prostatitis without positive cultures localizing a pathogen to the prostate, if no complicating factors such as bladder neck sclerosis, prostatic calculi, or urethral stricture were present. Practically no response to the treatment or deterioration was observed in patients with these complicating factors.

Tab. 2 Complement C3/coeruloplasmin per dl ejaculate before and after three ($p < 0.001$) and six months, respectively ($p < 0.001$; $p = 0.005$ comparing six vs. three months), of treatment in patients without complicating factors (CF) and before and after treatment in patients with CF ($p = 0.07$).

Complement C3/Coeruloplasmin	no CF			with CF	
	Pre N	3 months N	6 months N	pre N	post N
< 1,5mg/negative	–	3	11	–	–
1,5 – < 2,0mg / < 0,5mg	8	36	40	4	–
2,0 – 4,0mg / 0,5 – 1mg	46	30	13	11	9
3,0 – 8,0mg / > 1–3mg	17	2	5	1	7
missing values	1	1	3	2	2

*Details: see "Patients and Methods".

Most of the patients without CF experienced partial or complete relief from their complaints, and the findings on palpation of the prostate improved. The pollen extract led to a significant reduction of the L-VB 3 and of the concentration of complement C3 and coeruloplasmin in the ejaculate. This anti-inflammatory effect corresponded with a significant increase of the PUFRR. As revealed by the biometrical evaluation with $CCorr = 0.720$ and $rs = 0.565$, there is a high qualitative and quantitative inverse correlation between the changes of the L-VB 3 and the PUFRR.

Analyzing the ranked individual changes of both parameters and the absolute changes of the individual L-VB 3, a high increase of the PUFRR was registered together with high or very low decreases of the L-VB 3. This shows that also in patients with absent or minor inflammation in the prostate and thus with a small changing potential of the inflammatory parameter, the PUFRR increased markedly.

Obviously, complicating factors play an important role in the failure of the therapy with the pollen extract. The baseline values of the PUFRR were lower and those of the L-VB 3 were higher in these patients in comparison to the cases without CF, indicating a causal relationship with the presence of CF. Both parameters showed a deterioration from control values after treatment. Practically no patient with CF responded to the therapy with pollen extract. From this it seems reasonable to recommend a careful search for bladder neck sclerosis, prostatic calculi, urethral strictures, or other complicating factors in patients who do not improve after three months of therapy with the pollen extract.

According to Blenk and Hofstetter (9), complement C3 in ejaculate is a very sensitive indicator of an inflammatory process in the prostate or adnexae. It may also represent inflammatory alterations with minor and / or focal pathological changes within the gland which do not lead to a marked increase of the number of leucocytes in the prostatic expressate or in the VB 3. The comparison of the baseline values of complement C3/coeruloplasmin and of the L-VB 3 showed also in patients with a low number of leucocytes in VB 3 an increased concentration of complement C3 in the ejaculate. The similar course of these parameters, i.e., their continuous decrease, in patients responding to the treatment with pollen extract suggests that edema or inflammation may also be present in prostatodynia, as has been indicated by studies of patients with prostatodynia and BPH by Vahlensieck and Dworak (45) and di Trapani et al. (44). Echodense areas as a result of inflammatory processes are seen predominantly in submucous periurethral, but also in outer parts of the prostate gland (6). Kohnen and Drach (28) described an incidence of 98.1 % of inflammation in resected hyperplastic prostates and Gorelick et al. (21) found in the tissue cultures of 200 patients undergoing prostatectomy a positive, single organism, bacterial growth in 21 %.

By video-pressure-flow-EMG urodynamic investigations in a prospective study of patients with prostatitis syndrome, Barbalias (2) showed an increased MUCP. A distal and proximal narrowing in the "pars prostatica urethrae" was observed in several patients, and a synchronous decrease in urinary flow rates was recorded in the majority of cases. Thus, this functional urethral obstruction represents a common characteristic of patients with prostatodynia or non-bacterial prostatitis.

Barbalias (2) posits that in patients with non-bacterial prostatitis local inflammation may irritate adrenergic endings and result in high MUCP. Our finding of the inverse correlation between inflammation and uroflow supports this hypothesis, but, furthermore, the observed decrease of complement C3 allows us to assume that this mechanism of local irritation may be responsible in patients with prostatodynia, too.

Takeuchi et al. (42) reported a significant decrease of the MUCP from $92 \pm 23 \text{ cm H}_2\text{O}$ to $58 \pm 19 \text{ cm H}_2\text{O}$ ($x \pm \text{SD}$) with a reduction of the prostatic profile length and of prostatic urethral resistance (from $28 \pm 14 \text{ g / cm}$ to $12 \pm 3 \text{ g / cm}$; ($-x \pm \text{SD}$)) by pollen extract in patients with BPH. They concluded that this finding may be related to an elimination of edema or inflammation of the area in question.

It seems reasonable that the pathophysiology of voiding dysfunction due to an anatomical enlargement cannot be influenced except by removing the obstruction, but functional obstruction in the proximal or distal part of the "pars prostatica urethrae" may be decreased by the pollen extract leading to a similar, although restricted, response pattern in BPH as in the case of chronic prostatitis syndromes.

Thus, a common characteristic of BPH, chronic prostatitis, and prostatodynia may be the presence of edema or inflammation in the prostate and a functional urethral obstruction, which may explain the clinical efficacy of the pollen extract in these different nosological entities.

Cernilton ® is an extract from several pollens and can be pharmacologically characterized by a dose-dependent inhibition of the cyclo-oxygenase and 5-lipoxygenase reducing the biosynthesis of prostaglandins and leucotriens in vitro (30). In urethral strips of mice, Kimura et al. (26) and in rat urethral smooth muscle, Nakase et al. (33) observed a dose-related inhibition of noradrenaline-induced contractions by pollen extract. Furthermore, Ito et al. (25) and Habib et al. (23) reported growth inhibition by pollen extract of the rat prostate and in prostate cell cultures. According to this broad spectrum of pharmacodynamic properties the precise mode of action is unknown.

However, the course of clinical symptoms and signs and of the urodynamic and laboratory parameters with further improvement comparing the results after three and six months of therapy in this study suggest an important role of the inflammation. This seems to be confirmed by the observation of Buck et al. (14), who indicate that patients with chronic prostatitis syndromes may need at least three months of therapy with pollen extract before a significant response is achieved.

Regarding the still unsatisfactory therapeutic outcome in prostatodynia, non-bacterial prostatitis, and chronic bacterial prostatitis in the infection-free interval, this study shows encouraging results for patients with chronic prostatitis syndromes. Further investigations are necessary to elucidate the precise urodynamic impact of the clinical mode of action of Cernilton ®.

Summary

The results of a prospective case control study with the pollen extract Cernilton ®** in the therapy of 90 patients with chronic prostatitis syndromes are reported. Cernilton ® was given in a dose of one tablet three times daily for a period of six months. The following parameters were documented before and after three and six months of treatment: symptoms, findings on rectal palpation of the prostate, uroflow, leucocyturia in the midstream, and the first-voided 10-ml specimen after prostatic massage (VB 3), bacteriuria, and complement C3 / coeruloplasmin in the ejaculate.

Favorable results were obtained in the group of patients without associated complicating factors (N = 72): a response was observed in 56 (78 %) patients; 26 (36 %) were cured, and 30 (42 %) improved, with an increase in peak urine flow rate (ml / s) from 15.9 ± 5.2 to 23.5 ± 10.7 ($x \pm s$; $p < 0.001$), a reduction of leucocyturia in VB 3 from 50 to 20 leucocytes / μ l (median; $p < 0.001$), and a decrease of complement C3 / coeruloplasmin ($p < 0.001$) in the ejaculate. In cases with associated lower urinary tract pathology (N= 18), i.e., urethral strictures, prostatic calculi, bladder neck sclerosis, no response was observed with the exception of one patient who improved.

There was a strong qualitative (CCcorr = 0.720) and quantitative ($r_s = 0.565$) inverse correlation between the changes in leucocyturia in VB 3 and peak urine flow rate.

Treatment was discontinued because of clinical deterioration, mainly associated with symptomatic bacteriuria, or ineffective response in 13 (14,5 %) patients. The pollen extract was well tolerated in 96.7 % of cases. Three patients noted mild or moderate gastrointestinal symptoms, which did not lead to discontinuation of the therapy.

Regarding the common types of prostatitis syndromes, Cernilton ® is considered to be most effective in prostatodynia and nonbacterial prostatitis in patients without complicating factors. The correlation between the therapeutic improvement of uroflow and inflammation suggests their functional relationship in the pathophysiology of the disease and a smooth muscle relaxant (e.g., antiadrenergic) and / or anti-inflammatory mode of action of the pollen extract. Furthermore, if a patient fails to respond after three months of treatment with the pollen extract, a careful search for complicating factors is recommended.

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