Reviews in Endourology

Chronic Prostatitis/Chronic Pelvic Pain Syndrome: Is There a Role for Local Drug Infiltration Therapy?

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ABSTRACT

The clinical syndrome of chronic prostatitis ranges from well-defined chronic bacterial infections to poorly defined chronic pelvic pain syndrome (CPPS), previously referred to as “prostatodynia” or “abacterial prostatitis.” Faced with the obscure nature of the disease, its protracted course, and the poor response to oral medication, urologists have considered alternative routes of drug administration. We review the indications and outcomes of local drug infiltration (intraprostatic antibiotic and zinc, intrasphincteric botulinum toxin A, pudendal nerve blocks) and discuss their potential use and benefit in the treatment of chronic prostatitis syndromes.

INTRODUCTION

The clinical syndrome of chronic prostatitis ranges from well-defined chronic bacterial infections to poorly defined chronic pelvic pain syndrome (CPPS), previously referred to as “prostatodynia” or “abacterial prostatitis.” Faced with the obscure nature of the disease, its protracted course, and the poor response to oral medication, urologists have considered alternative routes of drug administration. We review the indications and outcomes of local drug infiltration (intraprostatic antibiotic and zinc, intrasphincteric botulinum toxin A, pudendal nerve blocks) and discuss their potential use and benefit in the treatment of chronic prostatitis syndromes.

INTRAPROSTATIC ANTIBIOTICS

Although bacteria are cultured in 10% or less of all cases of prostatitis, most urologists believe that treating chronic prostatitis and related syndromes with antibiotics confers benefit on a higher percentage of patients. In fact, antibiotics are the most commonly used treatment for chronic prostatitis, regardless of culture results. Patients with Category IIIA disease may also respond to antibiotics because of their anti-inflammatory effect, reduction of cytokine production, the neurotoxic effect of some antimicrobials (i.e., aminoglycosides), effects on bacterial strains that are not routinely cultured or not yet identified, or even by a strong placebo effect.

In order for a given antibiotic to be effective, it must reach
adequate concentrations within the prostate. Theoretically, after oral or systemic administration, only weakly acidic and lipidsoluble antimicrobials achieve high intraprostatic concentrations because the prostatic fluid pH increases with infection. With intraprostatic injections, on the other hand, therapeutic drug concentrations may be reached within the prostatic tissue independent of the pharmacokinetic and pharmacodynamic properties of the antibiotic. Other advantages of local injection include the absence of any limitation on the drug concentration and of inactivation by metabolism in the body. Therefore, the therapeutic window may be enhanced.

We identified six series of patients with chronic bacterial prostatitis (Category II) that was refractory to or recurrent despite adequate oral antimicrobials who were treated with intraprostatic injections of various antibiotics (Table 2). All infections were diagnosed using the Meares-Stamey four-glass test. Plomp and colleagues treated 29 patients with transperineal injection of thiamphenicol glycinate (2 g). Fifty-five percent of the patients achieved a negative culture of the prostatic fluid at 6 months with one or two infiltrations. An additional 10% required more than two infiltrations. Baert and Leonard also used the transperineal route to inject intraprostatic antibiotics in refractory chronic bacterial prostatitis in 24 patients. Cure was defined as negative prostatic fluid cultures and remission of symptoms for at least 6 months. Seventy-one percent of all patients were cured with one or two infiltrations, while 25% required several injections to obtain long-term remission. Seven patients (29%) relapsed after remission periods ranging from 13 months to 7 years. Jimenez-Cruz and coworkers treated 51 patients with intraprostatic amikacin (N = 27) or tobramycin (N = 24) weekly for 2 to 4 weeks. Injection was performed transperineally under ultrasound guidance in the

<table>
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<td>Recurrent and chronic infection</td>
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<td>Discomfort or pain in pelvic region for at least 3 months with variable voiding and sexual symptoms; no demonstrable infection</td>
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<tr>
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Samples are taken during the Stamey localization technique. EPS = expressed prostatic secretions; VB3 = postmassage voided bladder urine.

### Table 1. NIH Classification of Prostatitis

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### Table 2. Results of Intraprostatic Antibiotic Infiltration for Refractory Chronic Prostatitis (Category II)

<table>
<thead>
<tr>
<th>Series</th>
<th>No.</th>
<th>Age (range)</th>
<th>Drug, dose</th>
<th>Route</th>
<th>Cure definition</th>
<th>Cure rate with 1–2 cycles (%)</th>
<th>Percent requiring &gt;2 cycles to achieve cure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plomp et al 1980</td>
<td>29</td>
<td>52 (27–64)</td>
<td>Thiamphenicol 2 g</td>
<td>Transperineal, finger guided</td>
<td>Neg. culture PF at 6 months</td>
<td>55</td>
<td>10</td>
</tr>
<tr>
<td>Baert et al 1983</td>
<td>24</td>
<td>45 (29–63)</td>
<td>Gentamicin 2 x 80 mg, cephalosporin 3 x 1 g</td>
<td>Transperineal, finger guided</td>
<td>Neg. culture PF ≥6 months</td>
<td>71</td>
<td>25</td>
</tr>
<tr>
<td>Jimenez-Cruz et al 1988</td>
<td>51</td>
<td>NA</td>
<td>Amikacin 500 mg (27) or tobramycin 100 mg (24) for 2–4 weeks</td>
<td>Transperineal, US guided</td>
<td>Neg. culture PF at 3 and 6 months</td>
<td>70 and 59</td>
<td>NA</td>
</tr>
<tr>
<td>Yamamoto et al 1996</td>
<td>25</td>
<td>37 (28–57)</td>
<td>Amikacin 400 mg cephalosporin 2 g in 10 mL lidocaine 1%</td>
<td>Rectal, US guided</td>
<td>Neg. culture PF ≥12 months</td>
<td>56</td>
<td>28</td>
</tr>
<tr>
<td>Yavascaoglu et al 1998</td>
<td>37</td>
<td>42 (24–61)</td>
<td>Amikacin 500 mg</td>
<td>Suprapubic transvesical (19), transperineal (18)</td>
<td>Neg. culture PF at 12 months</td>
<td>44 + 7</td>
<td>NA</td>
</tr>
<tr>
<td>Hu et al 2002</td>
<td>50</td>
<td>NA</td>
<td>Amikacin 400 mg QD 10 times</td>
<td>Anal submucosal (30), IM (20)</td>
<td>Neg. culture PF at 3 months</td>
<td>33 + 5</td>
<td>NA</td>
</tr>
</tbody>
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PF = prostatic fluid; NA = not available.
The microbiologic cure indexes were 70% and 59% after 3 and 6 months, respectively, with one or two treatment cycles. The clinical cure rate was 43%, and 41% of the patients improved. No differences were observed between the two antimicrobials. Yamamoto et al reported on 25 patients with refractory chronic prostatitis treated with ultrasound-guided transrectal injections of amikacin and documented negative cultures of prostatic fluid beyond 12 months in 56% of the patients with one or two treatments; 28% of the patients required multiple infiltrations. Interestingly, the concentration of amikacin in the prostatic fluid 24 hours after the first intraprostatic injection, which was measured in five patients, exceeded the minimum inhibitory concentration of the causal organism, *E. coli*, by 1.3- to 4.7-fold. Yavascaoglu and associates randomized 37 patients with resistant prostatitis to receive local amikacin injections via a transperineal (N = 18) or suprapubic transvesical (N = 19) approach. The main reason for seeking an alternative route of injection was the pain and discomfort associated with the transperineal approach. At 1-year follow-up, the overall bacteriologic cure rate was similar for the two approaches (47% v 44%). Patients experienced less pain during access by the suprapubic route, but considerable difficulty was encountered in directing the needle to the prostate, and hematuria was observed more often. Hu and colleagues randomized 50 patients with chronic prostatitis to receive anal submucosal (N = 20) or intramuscular (N = 30) injection of amikacin 400 mg daily for 10 days. This is the only study that compared intraprostatic with systemic antibiotic. At 3 months, the cure rates were 33% compared with 5%. The authors claimed that this method of local injection is painless. Although the overall cure rate was lower than in previous studies, this controlled trial showed the superiority of local antibiotic injections to systemic treatment in chronic bacterial prostatitis. The microorganism cultured most frequently was *E. coli*, followed by other enterobacteria (*Klebsiella* spp, *Streptococcus faecalis*, etc.). The overall complication rate for local injection was low. Usually, multiple infiltrations were required to achieve adequate dispersion of the antibiotic solution in different directions of both prostatic lobes. Although painful, the procedure could be tolerated by most patients, and perineal discomfort usually subsided within 24 hours. Hematuria, dysuria, and hematopermia generally disappeared within 1 to 2 weeks. Although necrosis at the site of injection is a feared complication, it has not been reported recently.

Most of the aforementioned studies lacked long-term follow-up and did not incorporate a placebo arm. The natural history of the disease therefore could not be accounted for. It is also questionable whether the results are owing to systemic levels of the drugs. Hence, this technique did not gain widespread acceptance. Patients’ and physicians’ reluctance also may have played a role. Although acceptable results are shown initially, bacteriologic and symptomatic cure rates drop dramatically after 6 months. Local intraprostatic antibiotic injections remain a limited treatment option for only a subset of patients with chronic bacterial prostatitis, mainly those with refractory or recurrent disease despite adequate oral antimicrobials.

Mayersak explored this modality in 75 patients with “recalcitrant benign painful prostate syndrome” (CPPS; Category IIIA and B). The symptoms consisted of dysuria, urgency, perineal or suprapubic pain, rectal pain, nocturia, and urinary frequency. Culture of pathogens was not possible from urine or expressed prostatic secretions in 90% of the patients. A major criticism of this paper is that it did not document the inclusion criteria. Transrectal ultrasound-directed injection of gentamicin 160 mg (4 mL) and lidocaine 1% (2 mL) was used. Ninety percent of the patients were free of symptoms after one or two injections and 10% after multiple injections. The mean follow-up was not mentioned; however, those patients requiring four or five injections had a mean follow-up of 2.25 years (range 1–4 years). This casts doubt on treatment durability, as multiple injections were needed for those patients followed for more than 1 year. It also is debatable whether the therapeutic benefit could be attributed to the antibiotic or the anesthetic agent, as 90% of the patients experienced immediate relief of pain that the author himself attributed to lidocaine. Gentamicin may have also acted on the afferent limb of the pain circle by its neurotoxic effect on sensory nerve endings.

### INTRAPROSTATIC ZINC INJECTION

Secretory dysfunction of the prostate, characterized by an alteration in the composition of prostatic secretions, can be diagnostically significant. That is, a decrease in the zinc-containing prostatic antimicrobial factor among others. Zinc was one of the first antimicrobial factors identified in the seminal fluid. The finding that men with prostatitis had low levels of seminal fluid zinc prompted the recommendation of oral zinc supplements. However, oral intake of zinc does not seem to increase zinc levels in the seminal fluid. There are no clinical trials supporting the use of oral zinc in the prevention or treatment of chronic prostatitis.

Recently, intraprostatic injection of zinc has been studied in a rat model of infectious prostatitis. Microbiologic culture of the prostates demonstrated bacterial growth inhibition, and histopathologic study showed resolving prostatitis in the zinc-treated group but not in the control animals. Further studies from the same institution demonstrated that intraprostatic injection of zinc in normal rats increased and maintained prostatic zinc concentrations for 4 weeks and did not affect serum levels. No human studies are yet available, but it would be interesting to see if there is any synergistic effect between zinc and potent antimicrobials.

### PERIPROSTATIC BOTOX

Botulinum toxin A has been used for relief of voiding symptoms related to CPPS. Interrupting the efferent somatomotor branch of this central pain circle may offer an opportunity to treat chronic pelvic pain. Botox is an inhibitor of acetylcholine release at the neuromuscular junction of somatic nerves with striated muscle. Its has been successful in relieving a variety of conditions, including skeletal muscle spasms and spasticity, focal dystonia, wrinkles, detrusor-sphincter dyssynergia, and low-compliance neurogenic bladders.

Dysfunctional voiding whereby neurophysiologic obstruction results in high-pressure flow patterns has been implicated in the pathogenesis of CP/CPPS. Decreasing functional obstruction may reverse the pain circle. Maria and associates
treated four patients with transperineal botulinum toxin A infiltration (30 U). These patients suffered from chronic nonbacterial prostatitis and poor bladder emptying because of a spastic external urethral sphincter and had failed to respond to tamsulosin 0.4 mg once daily. Three patients showed continued improvement in their voiding at 8 weeks, as defined by a decrease in times to urinary flow (TQ) and maximum urinary flow rate (Qmax). Zermann and coworkers treated 11 patients having “chronic prostatic pain” with transurethral perinephritic injection of 200 U of botulinum toxin type A. Patients had suffered from pelvic floor tenderness, decreased conscious pelvic-control, urethral hyperalgesia, and urethral sphincter hyperactivity, as assessed by clinical evaluation, urodynamic studies, and cystoscopy to exclude other pathologies. The injection was followed by pelvic floor muscle weakening and relief of prostatic pain and urethral hypersensitivity hyperalgesia. Decreases in functional urethral length, urethral sphincter closure pressure, and postvoiding residual volume and increases in peak and average uroflow rates were documented.

Similarly, Phelan et al treated 21 patients having a variety of bladder outlet obstructions, including 12 with neurogenic detrusor-sphincter dyssynergia. After botulinum A injection, all but one of the patients were able to void without catheterization. Forty-seven percent of the patients reported significant subjective improvement in voiding at 3- to 16-months’ follow-up.

A potential side effect of Botox is spread to nearby muscles, particularly when large volumes are injected. Distant effects can occur, but generalized weakness is rare. Botox use should be well monitored in patients with neuromuscular junction disturbances or during treatment with aminoglycosides. Larger prospective controlled studies with long-term follow-up are warranted before conclusions are drawn on the value of this modality for the treatment of CP/CPPS. Botox injection may provide real improvement of some voiding symptoms and pain in patients with pelvic spasm in CP/CPPS or in patients with pseudodysynergia of the external urethral sphincter misdiagnosed as CPPS. Nevertheless, a trial of biofeedback should be offered first.

**PUDENAL NERVE BLOCK**

Possible pudendal nerve involvement in anorectal and pelvic pain dysfunction has received more attention in the proctology and gynecology literature than in urology. Pudendal neuropathy has been recognized as an etiologic factor in idiopathic vulvodynia, idiopathic proctalgia, and chronic constipation. Likewise, prostatic pathology might not be the principal source of urogenital, perineal, and anorectal pain in men believed to have CP/CPPS. Extraprostatic processes such as pudendal nerve compression deserve more attention from urologists.

The pudendal nerve (S2, S3, S4) originates from the lumbar sacral plexus and follows the pudendal nerve to the perineum. It leaves the pelvic cavity through the lesser sciatic foramen (between the sacrospinous and sacrotuberous ligaments) and runs on the internal surface of the obturator muscle, in Alcock’s canal. The pudendal nerve carries sensory neurons to the penis, perineum, and posterior scrotum and motor neurons to the muscles of the superficial perineal pouch and the external sphincter.

In an effort to elucidate the role of the pudendal nerve in pelvic pain syndrome, Robert and colleagues treated four patients with transperineal botulinum toxin A infiltration (30 U). These patients suffered from chronic nonbacterial prostatitis and poor bladder emptying because of a spastic external urethral sphincter and had failed to respond to tamsulosin 0.4 mg once daily. Three patients showed continued improvement in their voiding at 8 weeks, as defined by a decrease in times to urinary flow (TQ) and maximum urinary flow rate (Qmax). Zermann and coworkers treated 11 patients having “chronic prostatic pain” with transurethral perinephritic injection of 200 U of botulinum toxin type A. Patients had suffered from pelvic floor tenderness, decreased conscious pelvic-control, urethral hyperalgesia, and urethral sphincter hyperactivity, as assessed by clinical evaluation, urodynamic studies, and cystoscopy to exclude other pathologies. The injection was followed by pelvic floor muscle weakening and relief of prostatic pain and urethral hypersensitivity hyperalgesia. Decreases in functional urethral length, urethral sphincter closure pressure, and postvoiding residual volume and increases in peak and average uroflow rates were documented.

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**CONCLUSION**

Intraprostatic infiltration of antimicrobials for chronic prostatitis has shown acceptable cure rates only in nonrandomized and uncontrolled studies. It is to be emphasized that the level of current evidence is at best poor. Intraprostatic antibiotic infiltrations may therefore be used for chronic bacterial prostatitis refractory to oral medication, bearing in mind that long-term follow-up is not available. There are few data supporting its use in Category III CP/CPPS. Botox injections and pudendal nerve blocks are newer and interesting conceptual treatments for a subset of patients with refractory CP/CPPS. More research and clinical experience are required, however, before their addition to today’s armamentarium of CP/CPPS treatment options.

**REFERENCES**


