The Use of Testosterone in the Treatment of Chronic Postvasectomy Pain Syndrome: Case Report and Review of the Literature

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The purpose of this article is to describe a simple, intellectually reasonable, initial treatment for all subacute and chronic postvasectomy scrotal pains. The use of intramuscular testosterone cypionate in a dose of 400 mg monthly for 3 months is described for patients suffering from painful sperm granuloma at the vasectomy site or in the epididymis, circumventing the need for other medical or surgical approaches. Excellent results have been achieved in patients and a representative case is illustrated. The rationale for this approach based on endocrinological and immunological mechanisms is described.

Introduction

It is estimated that 500,000 to 1,000,000 vasectomies are performed for male sterilization annually in the United States representing a solution for 12% of all married couples. Excluding infidelity, early unprotected intercourse, or technical failure, the pregnancy rate following vasectomy is less than 0.1 per 100 women-years.\(^1\) Its applicability to the office setting and performance under local anesthesia lends itself to wide acceptance. Nevertheless, despite its advantages and acceptance, vasectomy has some well-known complications and remains an intellectually flawed procedure. Some complications of vasectomy are related directly to the surgical technique and include postoperative hemorrhage, vavaval reactions, postoperative infection, persistent motile or nonmotile sperm, poor patient selection resulting in intraoperative difficulty finding the vas, termination of the procedure due to pain, and rapid request for re-establishment of fertility through vasovasostomy.

Another complication, which is composed of a number of symptoms and physical findings, could best be grouped under the title of chronic postvasectomy pain syndrome (CPVPS). In older reviews of vasectomy outcomes, CPVPS has not been mentioned as a complication.\(^2\) However, in more recent articles regarding complications of vasectomy, chronic scrotal pain is now considered to be a negative factor in surgical outcome. In addition to various medical therapies, several inventive surgical procedures have been described to address this complication. Yet, the use of intramuscular (IM) testosterone to treat this condition is not mentioned in the literature and this shortcoming is difficult to explain given the nature of the problem, namely, the continued production of antigenic spermatozoa. Therapies which do not address this core issue are ineffective, misdirected, and possibly injurious. In military and civilian practices alike, chronic scrotal pains from a variety of sources are a frequent presenting symptom to the physician's office. A thorough diagnostic approach to all such pains is necessary, and, since the perplexing and contradictory solutions frequently overlap, they are included in this article.

Case Report

A 36-year-old patient presented with a history of having a vasectomy performed 6 years earlier. Approximately 6 months following his operation, he returned to the original urologist with complaints of a painful lump in the upper portion of the left side of the scrotum. After a course of antibiotics was unsuccessful, he sought the opinion of a second urologist who recommended excision of the mass. This second procedure of excision of a presumed sperm granuloma resulted in a pain-free state for approximately 5 years. The patient then developed pain in the left side of the scrotum and he returned to the second urologist who, after an unsuccessful course of antibiotics, recommended a left epididymectomy. At this point, the patient sought another option. On presentation, the patient had a slightly tender and enlarged left epididymis and slightly tender testicle and spermatic cord. On scrotal ultrasound, there was no evidence of varicocele, testicular tumor, or hydrocele. A course of testosterone cypionate 400 mg monthly IM for 3 months was recommended. The patient reported decrease in pain within 2 weeks and has been pain-free for more than 1 year after receiving the course of three injections.

Discussion

The incidence of CPVPS is reported to range from 0.1% to 54% depending on definitions of severity and duration. Choe and Kirkemo\(^3\) found 25.3% of patients to have chronic scrotal pains and epididymitis following vasectomy, of whom 70.6% reported occasional pain and 2.2% reported pain as sufficiently severe to cause an impact on the quality of life. They also emphasized the necessity of inclusion of chronic, postoperative pain in their vasectomy consent since pain has been the subject of litigation.\(^3\) The pain is due to the interruption of the efferent sperm ducts with continued sperm production resulting in either sperm granuloma at the vasectomy site and/or epididymal obstruction and granuloma.\(^4\)

A thorough history should be taken since CPVPS is defined as intermittent or constant; unilateral, bilateral, or alternating; and lasting more than 3 months. On initial presentation, the history of previous surgery is essential, for CPVPS is one possibility in the more generalized condition of various inguinal and scrotal pains. Troublesome pains preceding and following ingui-
nal herniorrhaphy, varicocelectomy, spermatocelectomy, and hydrocelectomy are well-known. In addition to previous surgery, a history should include symptoms related to infections due to epididymitis, prostatitis, and seminal vesiculitis, and inflammatory conditions such as interstitial cystitis. A history of trauma, possibly on the job injury, back pain, other chronic pain, and psychiatric disorders should be elicited. Chronic intermittent torsion, tumor, retroperitoneal fibrosis, periarteritis nodosa, epilpsey, self-palpation orchitis, aneurysms of the common iliac artery, intervertebral disc protrusion, diabetic neuropathy, gout, and pudendal nerve entrapment have been listed as potential causes of orchalgia. Vasectomy may have been performed long ago and questions should be asked directly to establish a possible cause.

On physical examination, tenderness is maximal about the epididymis; however, tenderness may be present in the spermatic cord, inguinal canal, and testis. The presence of a varicocele, testicular mass, hydrocele, sperm granuloma, spermatocele, or inguinal hernia should be sought. Referred pain from a kidney should be considered and ruled out.

A urinalysis and scrotal ultrasound are essential and should be ordered to establish the absence of microhematuria, nonpalpable tumor, varicocele, or epididymal mass. A noncontrast computed tomography scan of the abdomen and pelvis should be considered to determine any contribution of lithiasis, retroperitoneal mass, or vascular causes.

Treatments for scrotal pain in general and postvasectomy pain in particular should be directed toward their obvious causes. However, when the history, the physical examination, laboratory tests, and imaging studies result in pain as a diagnosis, treatments for pain are initiated. These treatments are medical and surgical and it is generally accepted that medical treatments should be tried first. Such medical treatments have included antibiotics, steroidal and nonsteroidal anti-inflammatory agents, antidepressants, narcotic analgesics, α-blocking agents, and anticonvulsants. Pain clinic consultation with resultant nerve blocks and neurostimulators, and psychiatric consultation are described. The problem of secondary gain from on-the-job injuries, litigation, and court settlements must be accepted as a detractor from any acceptable medical resolution. Surgical treatments have included excision of a sperm granuloma, epididymectomy, vasovasostomy, vasectomy, intratesticular injections, testicular denervation, microsurgical denervation of the spermatic cord, and decompression of the pudendal nerve. In general, articles describing surgical treatments are favorable toward their own approach. Davis et al. reported 34 patients with chronic scrotal pain of various etiologies. Of those treated with epididymectomy initially, 90% went on to have inguinal orchiectomy, and of those treated with inguinal orchiectomy, 73% experienced complete relief. In contrast, Costabile et al. analyzed 48 patients with chronic scrotal pain of undetermined etiology who underwent 74 different surgical procedures and found that of 31 available patients after 8 years, none had resolution of symptoms. Of those patients who underwent orchiectomy, 80% continued to complain of scrotal pain. Their conclusion was that invasive procedures should be avoided.

The neurological innervations of the testis, vas, and epididymis are complex and confusing due to parallel nomenclature for identical structures. However, only afferents are germane in this discussion. Somatic afferents from the tunica vaginalis and cremaster receive innervation originating in L1-L2 carried by the genital branch of the genitofemoral nerve to cell bodies in the dorsal root ganglia. Visceral afferents from the vas deferens, epididymis, and testis follow the spermatic vessels to branch to the inferior spermatic plexus, superior spermatic plexus, and inferior hypogastric plexus (sympathetics) of T10-L1. The pelvic splanchnic nerve (parasympathetic) carries afferents to the S2-S4 dorsal root ganglia. Although most visceral afferents have their cell bodies in the dorsal roots, some visceral afferents enter the spinal cord via ventral roots. It has been proposed that these afferents may participate in nociception. Sprouting between axons either at the level of the dorsal root ganglion or at the dorsal horn has been postulated as a cause of chronic, after injury pain with rerouting of signals from a light touch to a pain pathway. To prevent pathological pain from developing postvasectomy, injection of a local anesthetic into the abdominal side of the vas lumen during the procedure has been studied. It was postulated that sensitization of the dorsal horn can occur and subsequent tactile sensation can be carried via unmyelinated afferent C-fibers inducing painful sensation.

The dual functions of the testis, hormone production and spermatogenesis, are regulated by secretion of the pituitary gonadotrophins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH). In turn, the gonadotrophins are under the control of GnRH from the hypothalamus, with inhibitory feedback via steroid and peptide hormones from the testicle. LH stimulates the production of testosterone from the Leydig cells in the testis and FSH acts on receptors in the Sertoli cells. Although FSH is necessary for the normal development of the fetal testis, it appears to have an auxiliary role in spermatogenesis in adults since experimental evidence indicates spermatogenesis can proceed with testosterone stimulation alone. However, spermatogenesis cannot proceed without normal intra-testicular testosterone levels. Testosterone executes its effect on the Sertoli cell. The intratesticular testosterone concentration in humans is approximately 100 times higher than that in serum. A decrease of only 20% of normal in the intratesticular testosterone level in rats was sufficient to cause an arrest of spermatogenesis.

Exogenously administered testosterone has been proposed as a contraceptive in the male by suppressing LH and FSH from the pituitary. Two studies funded by the World Health Organization have shown that azoospermia can be produced by testosterone injections in 60% to 70% of Caucasians and 95% of Asian men. Severe oligospermia with counts of 3 million per milliliter occurred in the 30% of those who did not become azoospermic. Although reports state that this suppression is completely reversible, the testosterone rebound treatment for infertility is condemned due to the occasional conversion of oligospermia to permanent azoospermia through testosterone treatment. Although the ideal male contraceptive is yet to be developed, the efficacy of testosterone in the arrest of spermatogenesis is well-established.

IM, exogenous testosterone substitution for endogenous production would appear to be free of health risks—especially for the short-term. Oral agents, particularly the 17-alkylated derivative of testosterone were toxic to hepatocytes due to high first-pass
metabolism, are not recommended here. In hypotestosteronemic conditions, replacement with patches, gels, and buccal suppositories has had success. These administrative routes were not attempted here and have been less successful in inducing azoospermia and oligospermia in family planning studies than the IM route. The multisystem affects of testosterone are generally safe; however, absolute contraindications to administration would be breast carcinoma in men and prostate cancer. Relative contraindications include severe cardiac, renal, or hepatic disease, polycythemia, and sleep apnea.18

Aspermatogetic autoantigens are expressed only by germ cells and can elicit an immune response that causes diminished sperm production and damage to germ cells. The expression of these autoantigens postdate the early lymphocyte interactions that confer immunologic tolerance of self antigens. It is not until puberty that new antigenic expression takes place on maturing spermatozoa thereby rendering them foreign to the immune system. A major anatomic and physiologic mechanism for isolation of the testis immunologically is the blood-testes barrier: tight junctions at the apical regions of Sertoli cells isolate the luminal germ cells from immunologic surveillance. In humans, vasectomy as associated with the subsequent development of antisperm antibodies in approximately 50% to 80% of men. Although fertility can be re-established following vasectomy reversal, decline in fecundity has been ascribed to an increased prevalence of antisperm antibodies with time.19 Whether vasectomy was done with the testicular side open to allow a sperm granuloma to develop20 and relieve blow-out pressure on the epididymis, or sealed with clips, cauterezation, or ligatures with resultant sperm extravasation in the epididymis, it is certain that the normal epithelial barriers are breached. Additionally, the concern of autoimmunization to spermatozoa has been an ongoing concern in the best method for scrotal fixation of testicular torsion to prevent the possibility of future infertility although exposure is comparatively minor.21

The resultant exposure of sperm leads to macrophage phagocytosis and causes the individual to elicit responses to "self" antigens. Both humoral and cell-mediated responses are implicated in various inflammatory conditions. The presence of sperm granulomas has been noted on one or both sides in 40% of patients following vasectomy, and at vasectomy reversal in 30% to 60% of patients. Distention of the epididymis is uniformly seen during vasectomy reversal and ultrasound studies suggest postvasectomy sperm granulomas are common in the epididymis. These cream-colored nodules occurring at the severely dilated end of the vas or epididymis consist of a central mass of degenerating spermatozoa surrounded by a layer of epitheloid macrophages, surrounded in turn by loose connective tissue rich in lymphocytes and plasma cells. Analysis of fluid aspirated from symptomatic spermatoceles has yielded high levels of interleukin 6, interleukin 8, and tumor necrosis factor a, all proinflammatory cytokines.

Although the literature recognizes the association of intractable pain following vasectomy leading to recommendations for innovative but extensive medical and surgical treatments with less than total satisfaction, there is no mention of the use of testosterone to treat this condition. It appears that the relentless production of sperm with its associated antigenicity and pressure effects would best be served by the administration of testosterone for a brief period of time to eliminate the cause of the problem by the induction of severe oligospermia or azoospermia. Certainly, the resultant azoospermia of the testosterone rebound treatment is of no issue since the patient desired permanent sterility regardless. If the relief were to last for some period of time and recur, it could be easily repeated. No prohibition from other therapies is implied and they can certainly be performed if the patient was unresponsive to testosterone treatment.

The use of testosterone treatment is possible in other painful scrotal conditions in which occlusion of the efferent ducts is possible provided there is no contraindication, e.g., postoperative testicular pain in a patient with prostate cancer or a young male with pain from any of a variety of conditions if future fertility could be problematic.

Conclusion

Vasectomy is a common, effective, and permanent procedure for male sterility. Immediate and long-term complications have been well-described. In recent years, increasing concern and recognition of the CPVPS is apparent in articles describing vasectomy as a procedure and in methods, mainly surgical, to alleviate the unrelenting discomfort. The cause of the CPVPS is the continued production of sperm which are antigenic and provoke humoral and cellular antibody and inflammatory cytokine responses. No proposed method, surgical or medical, has addressed this cause, except for vasovasostomy, which defeats the purpose of vasectomy or is done in the face of proximal epididymal blow out and would be ineffective. Whether nociceptive reflexes or neuronal rerouting is independent or synergistic with these inflammatory responses remains to be determined. Testosterone cyprionate administered IM in 400 mg doses monthly for 3 months is an effective, frequently permanent, solution to this problem and should be used in all first-line cases of CPVPS. Why this has not been previously published is unknown.

References