Assessment of patient outcomes following submucosal injection of triamcinolone for treatment of Hunner's ulcer subtype interstitial cystitis

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COX M, KLUTKE JJ, KLUTLE CG. Assessment of patient outcomes following submucosal injection of triamcinolone for treatment of Hunner's ulcer subtype interstitial cystitis. The Canadian Journal of Urology. 2009;16(2):4536-4540.

Introduction and objective: *Hunner's ulcer subtype interstitial cystitis (IC) is characterized by the presence of circumscribed inflammatory ulcerations in the bladder wall identified during endoscopic examination of individuals with irritative voiding symptoms and pelvic pain. We present our experience with management of this subgroup with intralesional submucosal injection of corticosteroid.*

Methods: *Prospective analysis of patients presenting with Hunner's ulcer subtype IC was performed between November 2006 to April 2008. All patients underwent flexible cystoscopy and biopsy confirming the presence of Hunner's ulcer(s). Under general anesthesia, 10 ml of triamcinolone acetonide (40 mg/ml) was injected in 0.5 ml aliquots into the submucosal space of the center and periphery of ulcer(s) using an endoscopic needle. Patient symptoms and quality of life was assessed using two validated questionnaires, the International Prostate Symptom Score (IPSS) and the Pelvic Pain and Urgency/Frequency (PUF) symptom scale. Each questionnaire was administered prior to therapy and 4 weeks postoperatively. The postoperative interview included the Patient Global Impression of Change (PGIC).*

Results: *Thirty patients with Hunner's ulcer subtype IC underwent endoscopic submucosal injection of triamcinolone. The mean preoperative and postoperative IPSS were 21.1 and 11.3, respectively. The mean preoperative and postoperative PUF scores were 20.0 and 11.0, respectively. PGIC assessment revealed 21 of 30 patients (70%) very much improved. No perioperative complications were noted.*

Conclusion: *In Hunner's ulcer IC, submucosal injection of triamcinolone is well tolerated. This treatment offers significant improvement in symptoms and quality of life based on responses from validated questionnaires administered before and after therapy.*

Key Words: interstitial cystitis, Painful Bladder Syndrome, triamcinolone

Introduction

More than a century has passed since Max Nitze's cystoscopic description of a lesion in the bladder associated with profound, intractable urinary complaints.[1] As the microscopic appearance was of inflammatory cells extending into the submucosa, Nitze termed the disorder "Cystitis Parenchymatosa," and described it as a chronic bladder inflammation of unknown cause and no effective treatment. Subsequently termed Interstitial Cystitis (IC), the presentation of disabling symptoms of urgency, frequency, nocturia, and varying degrees of suprapubic discomfort, is one that the urologists will encounter

Accepted for publication December 2008

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not infrequently with estimates indicating that 197 of every 100,000 women and 41 of every 100,000 men in the United States are affected by IC.[2] IC is now recognized as a spectrum of diseases known as Interstitial Cystitis/Painful Bladder Syndrome (IC/PBS) characterized by symptoms of bladder pain, urgency, frequency, and nocturia in the presence of sterile urine cultures.[3,4] The lesion described by Nitze in 1907 and now referred to as Hunner's ulcer subtype IC is diagnosed by the cystoscopic finding of denuded epithelium, ulceration, and submucosal inflammation. It is reported to occur in 5%-20% of patients diagnosed with IC.[5,6] The pathogenesis of IC is still not clearly understood, and treatment options for patients with IC have varying degrees of efficacy. The purpose of this article is to present our experience with treating individuals with Hunner's ulcer subtype IC using submucosal injection of triamcinolone.

Materials and methods

The study protocol was approved by the Human Research Protection Office committee at Washington University in St. Louis. We performed a prospective analysis of patients presenting with symptoms consistent with IC between November 2006 and April 2008. One hundred patients were diagnosed with IC, of which 30 were subsequently diagnosed with Hunner'sulcer subtype IC. All patients had urgency, frequency, and chronic pelvic pain consistent with IC, and each underwent cystoscopic evaluation in the office with cold cup biopsy to confirm the presence of Hunner'sulcer(s). The majority of patients presented in the fifth and sixth decades of life and most had been evaluated elsewhere with as many as five treatments including hydrodistension, various bladder instillations, oral medication, and interstimtherapy. Patients were excluded if there was active urinary tract infection, history of bladder malignancy, or recent bladder surgery. Each procedure was performed under general anesthesia by a single surgeon in the ambulatory surgery center at one institution. After cystoscopic identification of the ulcer, 10 ml of triamcinolone acetonide injectable suspension (Kenalog) 40 mg/ml was injected in 0.5 ml aliquots into the submucosalspace of the center and periphery of the ulcer(s) using a 5 Fr Williams endoscopic injection needle (Cook Urological, Spencer, IN, USA). Patient symptoms and quality of life was assessed using two previously described validated questionnaires,[7,8] the International Prostate Symptom Score (IPSS) and the Pelvic Pain and Urgency/Frequency (PUF) symptom. Each questionnaire was administered prior to therapy and again 4 weeks postoperatively. The postoperative interview also included the Patient Global Impression of Change (PGIC), which patients were asked to rate their current symptoms as much worse, minimally worse, no change, minimally improved, much improved, or very much improved as to preoperative symptoms to determine subjective response to therapy. Individual patient preoperative and postoperative responses to questionnaire items were analyzed with the Wilcoxon rank-sum test.

Results

We prospectively identified 30 patients with Hunner'sulcer subtype IC. Each patient underwent biopsy confirming the diagnosis. Typical findings consisted of a moderately mixed inflammatory infiltrate that included the lamina propria and muscularis propria, and a portion of the urothelial layer was absent. The mean preoperative and postoperative IPSS were 21.1 and 11.3, respectively. The mean preoperative PUF score was 20; this corresponded to a mean PUF symptom score of 13.4 and a PUF bother score of 6.6. The mean postoperative PUF score was 11; this corresponded to a mean PUF symptom score of 7.8 and a PUF bother score of 3.2. Table 1 illustrates the mean changes in the IPSS and PUF symptom and botherscores. PGIC assessment revealed 21 patients (70%) very much improved, 5 much improved, 2 minimally improved, 1 with no change, and 1 patient who reported being very much worse after the procedure. No perioperative complications were noted. IPSS and PUF preprocedure and postprocedure scores showed statistical improvement following injection of triamcinolone. Table 2 illustrates the mean scores from the two questionnaires and the results of individual patient responses analyzed with the Wilcoxonrank-sum test. No analysis was possible with the PUF items regarding intercourse due to the majority of patients electing not to respond to this question.

TABLE 1. **Mean scores from validated questionnaire assessment indicating clinically significant improvement following submucosal injection of triamcinolone**

n= 30	IPSS	PUF symptom	PUF bother
Pre-injection	21.1	13.4	6.6
Post-injection	11.3	7.8	3.2

TABLE 2. **Mean preprocedure and postprocedure scores for individual questionnaire items and Wilcoxon rank sum analysis of cohort responses**

Question		Mean preprocedure score	Mean postprocedure score	p value
IPSS	Incomplete emptying	2.8	1.2	0.0001
	Frequency	4.0	2.0	< 0.0001
	Intermittency	2.1	0.9	0.0018
	Urgency	3.5	1.6	0.0001
	Weak stream	2.4	1.6	0.0287
	Nocturia	3.6	2.9	0.0055
	QOL	5.0	1.6	< 0.0001
	Total score	20.2	10.4	< 0.0001
PUF	Daytime voids	1.6	0.7	0.0003
	Nighttime voids	3.5	2.6	0.0004
	Nighttime voids bothersome	1.7	1.0	0.0018
	Symptoms during sex	1.7	1.1	n/a
	Avoid sex	1.1	0.6	n/a
	Pain in bladder, pelvis	1.8	1.0	0.0017
	Pain scale	2.2	1.0	< 0.0001
	Bother scale	2.0	0.7	< 0.0001
	Urgency after voiding	1.2	0.3	0.0007
	Urgency scale	2.2	1.3	< 0.0001
	Bother scale	2.0	1.1	0.0003
	Total pain score	13.4	7.8	< 0.0001
	Total bother score	6.6	3.2	< 0.0001
	Total PUF score	20.0	11.0	< 0.0001

Discussion

IC has a profound detrimental impact on patient quality of life in the domains of physical, emotional, social well-being and sexual function.[9-11] It is speculated that the prevalence of IC is higher than generally expected, and a recent article indicates the true prevalence of IC may be as high as one in 4.5 women.[12] Despite early awareness of the disease, many vital questions remain unanswered including the etiology of IC as well as a uniform algorithm for diagnosis and treatment of this disease.[13]

Although not necessary for diagnosis of IC, tissue biopsy is often performed to rule out malignancy or other potential disorders based upon cystoscopic appearance of the bladder.[14,15] The typical Hunner's ulcer is a stellate area of erythema with a pale center which bleeds when the bladder is distended, see Figure 1. Histologic examination of the Hunner's ulcer shows denuded epithelium, decreased mucin layer, inflammatory infiltrates, and pancystitis with mast cell invasion. Conversely, urothelial biopsies in nonulcerative IC shows an intact urothelial layer with scant inflammation.[16]

The pathogenesis of IC is not clearly understood, and various theories have been reported including "leaky epithelium" (epithelial dysfunction), mast cell activation, neural upregulation, and neurogenic inflammation leading to a self perpetuating process resulting in chronic bladder pain and voiding dysfunction.[17-20] An autoimmune role has also been suggested due to the clinical association with IC and other autoimmune diseases among affected families as well as the strong female preponderance of the disease.[21]

Accurate diagnosis of the subtype of IC is imperative for appropriate management.[22,23] Recent reports support the theory of IC as a constellation of symptoms in a broad spectrum of illness with multiple etiologies.[24,25] This may explain the complexity of the natural history of the disease process and the variation in response to medical therapy noted by many clinicians (i.e. Elmiron has less of an effect on ulcerative variety). Patients with nonulcerative IC are typically younger at diagnosis and symptom onset. Under general anesthesia, this group typically has a larger than expected bladder capacity.[26] Regulation of urinary nitric oxide synthase activity has been proposed to be of importance for immunological responses in IC and recent evidence suggests profound

differences between the two subtypes concerning nitric oxide production, mirroring the differences in inflammatory response with the highest levels of NO being identified in patients in the initial phase of ulcer variety IC.[27]

Multiple treatment options exist for IC with varying degrees of efficacy.[28] Oral therapies include NSAIDs, antidepressants, antihistamines, suplatast tosilate, and antibiotics. Intravesical management includes hydrodistension, intradetrussor injection of botulinum toxin, urinary alkalinization, and instillation of various compounds including resiniferatoxin, DMSO, BCG, pentosan polysulphate, oxybutynin, hyaluronan, heparin, and lidocaine. Refractory cases can be managed surgically with degrees of success with neuromodulation, supratrigonal cystectomy, and urinary diversion.[29-33]

Focal therapy for the management of the classic ulcerative form of IC has been reported in the literature. Transurethral resection of the Hunner'sulcer was described by Kerr in 1971. He reported relief of pain in 73% of patients, although the majority of successfully treated patients required a repeat resection at a later date.[34] The use of the Nd:YAG laser to resect the Hunner'sulcer has been reported to be 85% effective in eliminating pain. Recurrences with this modality are frequent and a 5% rate of bowel perforation was noted.[35]

Mast cells are multifunctional immune cells involved with innate immunity and are linked to autoimmune and neuroinflammatory disorders.[36-39] Recent evidence supports a central role of mast cells in the pathophysiology of IC.[40] The hallmark of ulcer variety IC is focal visible full thickness inflammation of the bladder. Steroids have been shown to have a vital role in the treatment of many autoimmune and inflammatory diseases. However, systemic corticotherapy has many known side effects including diabetes, weight gain, osteoporosis, high blood pressure, and mood disorders.[41] An alternate means of obtaining the steroid response is focal administration. Steroid injection into a visible bladder ulcer was first reported by Johnston in 1956.[42] Triamcinolone is a synthetic glucocorticoid with anti-inflammatory action and has an extended duration of effect which may be sustained over a period of several weeks.[43] Triamcinolone acetonide has been demonstrated to be safe[44] and has been used extensively in many ophthalmic procedures as an adjunct for postoperative inflammation.[45,46]

In our practice, the majority of patients with IC are referred by other providers due to failure to achieve satisfactory control of symptoms using standard interventions. The Hunner'sulcer subtype makes up a significant proportion of these patients, especially in the older female patient, and pain is the most bothersome component. The strengths of our study include the prospective nature of the data collection and the objective evaluation of symptoms using validated questionnaires. Although not validated for IC patients, we chose to include the IPSS questionnaire in our female cohort because it was readily available in our clinic, easy to understand and administer, and the components of the questionnaire focused upon urinary symptoms common to IC patients as well. One potential weakness of this study is the relatively short follow up period. Although the majority of patients continued to have good symptom control, two patients required repeat injection during the study period indicating the duration of efficacy of submucosal triamcinoloneto be at least 7 months. We expect a 1 year response in terms of symptom relief for most patients based upon preliminary data, at which time repeat injections are given with similar response. Our cohort will continue to be evaluated periodically to better assess this issue. Our work does represent the first report of local management of Hunner's ulcer subtype IC utilizing triamcinolone injection into the ulcer with objective data confirming symptomatic control and improved quality of life in a population with a difficult disease process. Interstitial cystitis is a complex disease and a diagnosis with multiple exclusion criteria, and one must be vigilant to rule out potentially life threatening conditions such as carcinoma in situ. Once this has been accomplished, the goal of the therapeutic intervention should be to maximize efficacy while minimizing adverse events and morbidity of the procedure. No perioperative or late complications were noted among our patient population.

Conclusions

We believe our experience with the management of Hunner's ulcer IC using submucosal injection of triamcinolone illustrates a novel approach to a disease that is often refractory to standard medical therapies for nonulcerative IC. This treatment is well tolerated and offers clinically and statistically significant improvement in symptoms and quality of life for a select group of IC sufferers based on responses from validated questionnaires administered before and after therapy. □

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