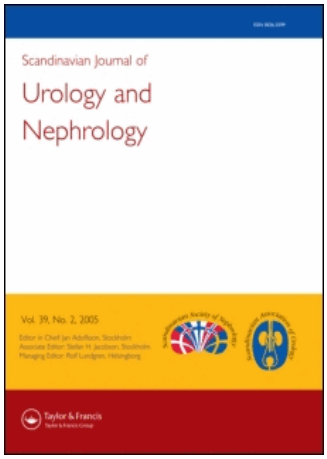

Scandinavian Journal of Urology and Nephrology
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713692219

A rational combination of intravesical and systemic agents for the treatment of interstitial cystitis

Rajesh Taneja [a]; Kailash K. Jawade [b]
[a] Senior Consultant Urologist and Coordinator, Pushpawati Singhania Research Institute, New Delhi, India
[b] Senior Resident Surgical Division, Pushpawati Singhania Research Institute, New Delhi, India

First Published on: 28 June 2007
To cite this Article: Taneja, Rajesh and Jawade, Kailash K. (2007) 'A rational combination of intravesical and systemic agents for the treatment of interstitial cystitis', Scandinavian Journal of Urology and Nephrology, 41:6, 511 - 515
To link to this article: DOI: 10.1080/00365590701435918
URL: http://dx.doi.org/10.1080/00365590701435918

Scandinavian Journal of Urology and Nephrology, 2007; 41: 511–515

ORIGINAL ARTICLE

A rational combination of intravesical and systemic agents for the treatment of interstitial cystitis

RAJESH TANEJA[1] & KAILASH K. JAWADE[2]

[1]*Senior Consultant Urologist and Coordinator, and* [2]*Senior Resident, Surgical Division, Pushpawati Singhania Research Institute, Press Enclave Road, Sheikh Sarai, Phase II, New Delhi, India*

Abstract

Objective. Interstitial cystitis is a condition with a poorly understood etiology and, consequently, various treatment options have been described in the literature, with a less than optimal outcome. The aim of this study was to examine the role of a combination of intravesical hydrocortisone and heparin, together with oral bladder sedatives and systemic triamcinolone, for the treatment of interstitial cystitis. *Material and methods.* A total of 26 patients who were diagnosed as having interstitial cystitis were treated with weekly intravesical hydrocortisone (200 mg) and heparin (25 000 IU) in physiological saline for 6 weeks. In addition, they were given oral bladder sedatives such as oxybutynin or tolterodine. Ulcerative, refractory and recurrent cases were treated with intramuscular triamcinolone (40 mg) weekly for 6 weeks. *Results.* All patients experienced an improvement in symptoms within 48 h of their first intravesical instillation. While 19 patients (73%) experienced almost complete pain relief, five of the remaining seven patients improved with intramuscular triamcinolone. Frequency reduced from a mean of 23.2 to 10.9 voids per day and was acceptable in 21 patients (80%). Six patients (23%) had a relapse of symptoms in the form of pain and were treated satisfactorily by means of intramuscular triamcinolone. The mean duration of follow-up was 18.3 months. *Conclusion.* A combination of intravesical hydrocortisone and heparin, along with oral bladder sedatives and systemic steroids, has been used with encouraging results in a small group of patients with interstitial cystitis.

Key Words: *Interstitial cystitis, intravesical hydrocortisone*

Introduction

Interstitial cystitis (IC) is a chronic non-infectious inflammatory condition characterized by a wide spectrum of clinical presentations, including pelvic pain and irritative lower urinary tract symptoms with or without evidence of hematuria. It is an uncommon clinical condition which presents as painful bladder syndrome and is often missed, leading to avoidable complications and undue suffering. Pain is usually felt more with a full bladder and subsides after urination. It has been suggested [1] that men with non-bacterial prostatitis may actually represent part of the spectrum of clinical presentations of IC. The symptoms arising from IC may be so severe and frustrating as to cause depression, social isolation and eventually loss of productive working hours, culminating in deterioration of quality of life. Therefore, treatment of IC requires all aspects of the condition to be focused on.

As the diagnosis of IC is primarily a diagnosis of exclusion, it is essential to exclude other conditions that mimic IC. There are two varieties of IC: classic and non-ulcerative. Presently [2] there is no evidence to suggest that the non-ulcerative variety may progress to the ulcerative variety. Defective epithelial permeability due to a lack of surface glycosaminoglycans (GAGs) is considered to be one of the etiological factors for IC [3]. This increased permeability causes back-diffusion of urea and other solutes into the sub-epithelial layer, leading to pancystitis [4]. The demonstration of sheets of plasma cells, aggregates of T cells and B-cell nodules in biopsy samples obtained from the bladder wall is suggestive of an autoimmune phenomenon as a causative factor of IC [5].

Correspondence: Rajesh Taneja, Surgical Division, Pushpawati Singhania Research Institute, Press Enclave Road, Sheikh Sarai, Phase II, New Delhi 110017, India. Tel: +91 11 29252516. Fax: +91 11 29250548. E-mail: rajeshtanejadr@rediffmail.com

(Received 11 August 2006; accepted 19 March 2007)

ISSN 0036-5599 print/ISSN 1651-2065 online
DOI: 10.1080/00365590701435918

Theories of neurogenic inflammation have also been applied to explain the perpetuation of the pain–inflammation cycle [6].

Numerous treatment options have been described in the literature [7–11], including oral agents such as non-steroidal anti-inflammatory drugs, narcotics, antihistamines, pentosan polysulfate, tricyclic antidepressants, gabapentin and immunosuppressive agents. Intravesical instillation of dimethyl sulfoxide has been shown [12] to have a very good immediate response in up to 93% of patients with IC. However, there was a high relapse rate during the next 4 weeks. In a later study by the same group [13], it was demonstrated that the addition of heparin led to longer periods of remission. Heparinoids (heparin, pentosan polysulfate) have been shown to downregulate the sensory nerve endings by gradually restoring the barrier function of the urothelium [11]. In view of the inflammatory nature of the disease, anti-inflammatory agents are expected to ease the symptoms of IC. Hydrocortisone is one such quick-acting anti-inflammatory corticosteroid. As the urothelial barrier is weak in patients with IC, it is only logical to use the intravesical route for hydrocortisone. Based on this reasoning we conducted this study to test the clinical efficacy of an intravesical solution of hydrocortisone and heparin, together with systemic agents, for the treatment of 26 cases of IC.

Material and methods

Between April 2001 and October 2005, patients presenting to the outpatient department of a tertiary care hospital with suprapubic pain, dysuria and irritative voiding symptoms for >3 months were evaluated clinically with a high index of suspicion for IC. A detailed history was obtained to exclude urinary tract infection, calculus disease and a past history of anti-tubercular treatment. The exclusion criteria are listed in Table I. A frequency–volume record was obtained to assess the functional bladder capacity. Clinical examination included a note of mental status and behavioral abnormalities. A focused neurological examination, including assessment of perineal sensation, muscle power in the lower limbs, deep tendon reflexes and muscle tone, was carried out in all cases. Examination of the external genitalia in males and the pudenda in females was carried out to exclude local treatable pathology contributing to the symptoms. Microscopic examination of urine was performed and a sample was saved for pyogenic culture. A cytological examination of the sediment of the spun urine sample was done to look for malignant cells if there was gross hematuria. If urine analysis revealed pus cells but the pyogenic culture was sterile, patients were excluded and investigated for tuberculosis. Fasting blood sugar and serum creatinine values were routinely determined, along with complete blood counts for all patients. Screening ultrasonography of the urinary tract was done in all cases to exclude calculus disease, bladder polyps and any other anomaly. A note was made of the full bladder capacity and the post-void residual urine volume. In addition, uroflowmetry studies were conducted in male patients to evaluate their voiding function.

Table I. Exclusion criteria.

Duration of symptoms <3 months
Evidence of infection on microbiological examination of voided urine specimen
Untreated calculus disease
Neurological disease which may have a causal relationship to symptoms
History of anti-tubercular treatment
Malignancy of urinary tract
Bladder outlet obstruction

Patients in whom no clinical indicators of other diseases were found were subjected to cystopanendoscopy under general anesthesia. The urethra and bladder neck were routinely inspected and an initial impression of the bladder interior was made. Hypervascularity, multiple arborizing vessels, stellate scars and mucosal ulceration (if any) were looked for. A note was also made of the approximate bladder capacity. Post-decompression petechial hemorrhages and 'raining of blood' were specifically looked for. A biopsy was performed using cold cup biopsy forceps in all cases. This was taken from the edge of the ulcer (if present) and from the most inflamed area in other cases. In all cases the site of biopsy was coagulated using a Bugbee™ electrode. In the initial two cases, standard hydro-distension was done for 8 min at a pressure of 80 cmH_2O. However, due to significant postoperative hemorrhage this was not done in subsequent cases. All patients were given oral ciprofloxacin (500 mg every 12 h) beginning on the morning of the procedure and for up to 72 h afterwards. The patients were grouped as 'classic' or 'non-ulcer' cases depending on the presence or absence of mucosal ulcers on cystoscopy.

After obtaining a histopathological diagnosis suggestive of non-specific cystitis, patients were administered an intravesical instillation of a solution of heparin (25 000 IU) and hydrocortisone (200 mg dissolved in 50 ml of physiological saline) every week for 6 weeks. For intravesical instillation, a 10 Ch disposable soft catheter was used under aseptic conditions. The patients were asked to empty their bladder just beforehand and not to urinate for at

least 1 h after the instillation (contact period). During this time, they were instructed to adopt supine, prone and both lateral positions for 15 min each. Oral antimuscarinic agents such as oxybutynin hydrochloride (5 mg twice a day) or tolterodine (4 mg once a day) were added to reduce the frequency of urination. These medications were continued throughout the follow-up period.

Fasting blood sugar was monitored on alternate days in patients who had pre-existing diabetes mellitus, and every fortnight for the other patients. A urine culture was done 1 week after the last intravesical treatment. All patients were re-examined in the outpatients department every fortnight for the first 3 months and every 3 months thereafter. A note was made of reductions in pain and frequency. Patients who had ulcerative lesions on cystoscopy and those who had a partial improvement in pain received intramuscular (i.m.) triamcinolone (40 mg) once a week every week for 6 weeks beginning with the last dose of the intravesical treatment. Patients who presented with a recurrence of symptoms during the follow-up period also received a weekly injection of triamcinolone (40 mg i.m.) for 6 weeks. One patient required a repeat course of intravesical instillation.

Results

Having excluded other diagnosable causes of pelvic and perineal pain, along with irritative lower urinary tract symptoms, a total of 26 patients (23 females, 3 males) who were clinically suspected of having IC were enrolled. The mean age at presentation was 52.2 years (range 40–72 years). The duration of symptoms ranged from 2 to 10 years (mean 6.8 years). Pain in the lower abdomen and dysuria were present in all cases. Troublesome frequency of urination ranged from once every hour to every 15 min and was characterized by unexplained episodes of exacerbation. Terminal hematuria was noted in three patients. The functional bladder capacity, as assessed by means of frequency–volume charts, was found to be markedly reduced (mean value 158 ml). Comorbidities encountered included anxiety neurosis ($n=14$), diabetes mellitus ($n=6$), bronchial asthma ($n=3$) and thyrotoxicosis ($n=1$). Routine urine examination revealed microscopic hematuria in seven patients, with a conspicuous absence of pus cells or casts.

On cystoscopy, all patients had increased vascularity of the bladder mucosa with petechial hemorrhage. All patients conformed to the diagnostic criteria laid down by the National Institute of Diabetes, Digestive and Kidney diseases for the diagnosis of IC. Stellate scars were seen in 14 cases, in whom an active ulcerative process was seen in three. It is interesting to note that these three patients had reported having hematuria on termination of voiding during the clinical interview. Cold cup biopsy from the bladder mucosa was reported to demonstrate a chronic non-specific inflammatory exudate in the form of a dense infiltration of lymphocytes and monocytes into the lamina propria and muscularis mucosa.

All patients experienced an improvement in pain within 48 h of their first intravesical instillation. At the end of the sixth instillation, 19/26 patients (73%) had almost complete pain relief. In the remaining seven patients, including the three with ulcerative lesions, an i.m. injection of triamcinolone 40 mg was added as a weekly supplement for 6 weeks. The pain became tolerable in five of these seven patients. Four patients (all from the earlier part of the series) received oxybutynin, while 22 received tolterodine throughout the follow-up period. Oral treatment did not need to be discontinued in any of the patients due to side-effects. Frequency reduced from a mean of 23.8 to 10.6 voids/day and was acceptable to 21/26 patients (80%) (Table II).

Although blood sugar levels in diabetic patients did not change with intravesical treatment, derangement of glycemic control occurred in both diabetic patients who received systemic triamcinolone, which was easily managed with appropriate adjustment of medication. None of the patients developed bacteriuria as documented by microbial culture reports of the voided urine samples collected 1 week after the end of the intravesical treatment schedule. Six patients relapsed with symptoms of dysuria and suprapubic pain. While one relapsed after 2 years, others relapsed after 3–6 months of follow-up. Three of these patients had required i.m. triamcinolone at the end of the intravesical instillation, while the other three had responded well to initial intravesical treatment alone. All these patients were managed with i.m. triamcinolone (40 mg weekly for 6 weeks), with good results. One of them, who had initially relapsed at 3 months, reported a second relapse after another 4 months. She was treated with another course of six intravesical instillations of the same solution and has remained pain-free for 4 months at present. The mean duration of follow-up was 18.3 months (range 6–60 months).

Discussion

A high index of suspicion is the key to diagnosing IC. However, other diseases, such as tuberculosis, carcinoma in situ, eosinophilic cystitis, neurogenic bladder, drug-induced cystitis, detrusor endometriosis and radiation cystitis, should be excluded.

Table II. Patient profiles and response to treatment.

Patient No.	Age (years)	Sex	Cystoscopic picture	Functional bladder capacity (ml)		No. of voids per day		Pain relief
				Pretreatment	Post-treatment	Pretreatment	Post-treatment	
1	44	F	Non-ulcer	120	250	24	12	Complete
2	62	F	Ulcer	150	300	22	12	Satisfactory
3	48	F	Non-ulcer	70	200	36	22	Complete
4	54	F	Non-ulcer	180	240	20	10	Complete
5	52	F	Non-ulcer	200	250	18	8	Satisfactory
6	48	F	Non-ulcer	140	250	24	10	Complete
7	63	F	Non-ulcer	180	240	20	8	Complete
8	57	F	Non-ulcer	130	210	26	12	Satisfactory
9	72	F	Non-ulcer	50	200	42	20	Complete
10	68	M	Non-ulcer	200	300	18	8	Inadequate
11	56	F	Non-ulcer	230	350	16	8	Complete
12	46	F	Non-ulcer	230	400	18	6	Complete
13	42	F	Ulcer	170	240	24	10	Satisfactory
14	66	F	Non-ulcer	240	400	20	6	Complete
15	49	F	Non-ulcer	150	300	32	16	Inadequate
17	45	F	Non-ulcer	280	380	16	6	Complete
18	52	F	Non-ulcer	180	250	22	12	Complete
19	44	F	Non-ulcer	200	300	26	8	Complete
20	52	M	Non-ulcer	180	240	22	10	Complete
21	55	F	Non-ulcer	180	300	24	6	Complete
22	49	F	Non-ulcer	160	240	24	10	Complete
23	63	F	Ulcer	60	200	34	14	Satisfactory
24	45	F	Non-ulcer	70	180	36	16	Complete
25	68	F	Non-ulcer	200	300	20	10	Complete
26	58	F	Non-ulcer	160	350	24	8	Complete
			Mean	158.0	264.2	23.8	10.6	

Longstanding cases of IC occur as 'burnt-out bladder' or 'end-stage bladder disease'. The cause of the symptoms of IC is inflammation and subsequent fibrosis of all layers of the urinary bladder. The inflammation is presumably due to a defective urothelial barrier, which allows urinary constituents to cause an inflammatory response in the layers of the urinary bladder. The GAG layer forms the primary component of the urothelial barrier, and becomes depleted in cases of IC. Heparinoids and certain dietary supplements, such as chrondroitin sulfate and sodium hyaluronide, have been used to replenish this GAG layer [14]. Intravesical heparin alone has been reported to be effective in 50% of patients [15]. However, heparin takes time to mend the urothelial barrier and continuing inflammation may delay or even perhaps adversely affect this process. In addition, inflammation keeps upregulating the sensory nerve endings in the bladder, thus potentiating neurone-mediated inflammation [11,13].

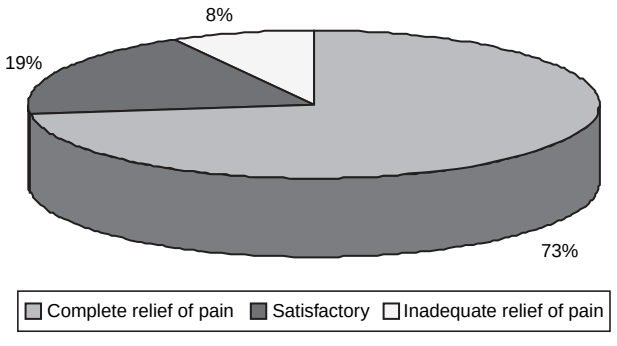

Figure 1. Pain relief in response to treatment.

The results of our study tend to confirm this hypothesis as intravesical instillation of hydrocortisone as an anti-inflammatory agent, along with heparin, was able to reduce symptoms quickly and for long periods of time. Downregulation of bladder sensory nerve endings with a combination of heparin and lignocaine has been shown [11] to have an almost instantaneous effect. In the present study, systemic triamcinolone was used in resistant cases and in patients with ulcerative IC, with favorable results. Use of systemic steroids has also been advocated by Soucy et al. [16]. In our study, follow-up indicated sustained relief of symptoms for a mean duration of 18.3 months. Patients who relapsed clinically responded well to systemic triamcinolone. However, these patients reported a recurrence of symptoms, albeit mild in nature. Only one of these patients required repeat intravesical treatment for a second relapse. She perhaps had a very

aggressive disease process and therefore required repeat treatment.

In the present study, no attempt was made to assess the influence of various dietary ingredients on urinary frequency. Although pain was very well treated with this modality, frequency was reduced only to tolerable limits. A reduction in frequency tended to correlate inversely with the chronicity of the disease. The longer the pretreatment duration of symptoms, the greater the residual frequency, perhaps due to a more extensive fibrotic reaction in the detrusor and a consequent reduction in bladder capacity. The exact contribution of each individual agent, i.e. the intravesical instillation and the oral anti-muscarinic drug, in reducing frequency could not be determined in this study. A double-blind, placebo-controlled study may be conducted to study the individual efficacy of these agents in reducing frequency. The present study was conducted to test the clinical response in cases of IC treated with a rational combination of pharmacological agents. It did not compare the efficacy of the combination of intravesical hydrocortisone and heparin vis-à-vis various agents used by other workers.

Conclusions

IC is much better understood today and innovative treatment modalities are increasingly being reported. In this study, clinical use of intravesical heparin and hydrocortisone along with systemic treatment was shown to be quite effective in terms of reducing symptoms to satisfactory levels for an adequate period of time in a small group of patients. However, a larger randomized trial may be designed to further document the efficacy of this treatment modality.

References

[1] Parsons CL. Prostatitis, interstitial cystitis, chronic pelvic pain and urethral syndrome share a common pathophysiology: lower urinary dysfunctional epithelium and potassium recycling. Urology 2003;62:976–82.

[2] Koziol JA, Adams HP, Frutos A. Discrimination between the ulcerous and the nonulcerous forms of interstitial cystitis by non-invasive findings. J Urol 1996;155:87–90.

[3] Hurst RE, Roy JB, Min KW, Veltri RW, Marley G, Patton K, et al. A deficit of chondroitin sulfate proteoglycans on the bladder uroepithelium in interstitial cystitis. Urology 1996; 48:817–21.

[4] Parsons CL, Lilly JD, Stein P. Epithelial dysfunction in non-bacterial cystitis (interstitial cystitis). J Urol 1991;145: 732–5.

[5] Harrington DS, Fall M, Johansson SL. Interstitial cystitis: bladder mucosa lymphocyte immunophenotyping and peripheral blood flow cytometry analysis. J Urol 1990;144:868J.

[6] Pang X, Marchand J, Sant GR, Kream RM, Theoharides TC. Increased number of substance P positive nerve fibres in interstitial cystitis. Br J Urol 1995;75:744–50.

[7] Mayer R, Propert KJ, Peters KM, Payne CK, Zhang Y, Burks D, et al. A randomized controlled trial of intravesical bacillus Calmette-Guerin for treatment of refractory interstitial cystitis. J Urol 2005;173:1186–91.

[8] Payne CK, Mosbaugh PG, Forrest JB, Evans RJ, Whitmore KE, Antoci JP, et al. Intravesical resiniferatoxin for the treatment of interstitial cystitis: a randomized, double blind, placebo controlled trial. J Urol 2005;173:1590–4.

[9] Phatak S, Foster HE Jr. The management of interstitial cystitis: an update. Nat Clin Pract Urol 2006;3:45–53.

[10] Moldwin R, Sant GR. Interstitial cystitis: pathophysiology and treatment update. Clin Obstet Gynecol 2002;45:259–72.

[11] Parsons CL. Successful down regulation of bladder sensory nerves with combination of heparin and alkalinized lidocaine in patients with interstitial cystitis. Urology 2005;65:45–8.

[12] Perez-Marrero R, Emerson LE, Feltis JT. A controlled study on dimethyl sulfoxide in interstitial cystitis. J Urol 1988;140: 36–9.

[13] Perez-Marrero R, Emerson LE, Maharajh DO, Juma S. Prolongation of response to DMSO by heparin maintenance. Urology 2003;41(1 Suppl):64–6.

[14] Theoharides TC, Sant GR. A pilot open label study of Cystoprotek in interstitial cystitis. Int J Immunopathol Pharmacol 2005;18:183–8.

[15] Parsons CL, Housley T, Schmidt JD, Lebow D. Treatment of interstitial cystitis with intravesical heparin. Br J Urol 1994;73:504–7.

[16] Soucy F, Gregoire M. Efficacy of prednisone for severe refractory ulcerative interstitial cystitis. J Urol 2005;173: 841–3.