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Clinical experience with multiagent intravesical therapy in interstitial cystitis patients unresponsive to single-agent therapy

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Summary. A total of 25 patients with the diagnosis of interstitial cystitis (IC) were involved in this study. All patients had been previously diagnosed with interstitial cystitis and had received treatment with single intravesical agents. Patients were divided into two groups according to their bladder capacity. The bladder capacity was >350 ml in group I patients and <350 ml in group II patients. For our study, dimethylsulfoxide (DMSO), methylprednisolone, and heparin sulfate were given every week for a total of 6 weeks. When symptoms recurred, supportive oral pharmacotherapy consisting of anticholinergics and/or tricyclic antidepressants was given. Under anesthesia, patients in group I showed a 99% increase in their bladder capacity; whereas those in group II showed an increase of only 19%. Cystoscopically, Hunner's ulcers were present in 60% of the group II patients but were seen in only 5% of the group I patients. Histopathological examination showed that the inflammatory changes were more frequent and severe in group II than in group I. Mast-cell hyperplasia was present in 100% of the patients in group II, versus only 61% of those in group I. A total of 23 patients (92%) achieved an initial remission averaging 8.1 months. In all, 9 patients (35%) had 1 or more relapses, and all achieved a subsequent remission averaging 8 months. By this combined multiagent approach, the majority of patients with IC obtained relief from their incapacitating symptoms and were socially rehabilitated.

Few diseases prove as difficult to diagnose and as difficult to treat as interstitial cystitis (IC). Afflicted patients suffer from incapacitating urgency, frequency, nocturia, and pain. Quality-of-life scores measured in these patients have been lower than those recorded for patients with chronic renal disease [1]. Patients are understandably frustrated when told they have a disease of unknown etiology, a disease with no cure. Since the exact etiology and a specific cure are as yet unknown, we developed a protocol that uses intravesical multiagent therapy supplemented by oral medications as needed. An essential part of the program is a group of supportive compassionate personnel, incuding physicians and nurses who can translate their own confidence into optimism and hope for these desperate patients.

The problems of IC in women are estimated to occur in between 18 and 36 per 100,000. The female-to-male ratio is 10 to 1 and the average age at diagnosis is between 40 and 50 years [2]. Very few blacks have been diagnosed with IC. The average interval from the onset of symptoms to diagnosis has been 24–51 months; this interval has recently been reduced due to more awareness of physicians and patients with the disease. Although the majority of patients are middle-aged and white women, both children and the elderly may be afflicted. Several etiological theories have been proposed. Among those that have been explored are infections [3, 4], exposure to toxic substances in the urine [5], autoimmune disease [6–11], hypersensitivity reaction to local stimulants [12, 13], neurogenic or vascular inflammation [14–18], and psychosomatic origin [19, 20]. Despite much research, the etiology remains elusive. Considerable attention has focused on the possibility that the protective glycosaminoglycan (GAG) lining the transitional epithelium leaks, allowing toxic substances to penetrate the deeper layers and induce an inflammatory response [21–23]. Nonetheless, the reported success of heparin-like agents seems logically based on their ability to simulate this GAG-defense layer [24, 25]. Additionally, the success of the time-tested dimethylsulfoxide (DMSO) in the treatment of IC probably lies in its anti-inflammatory properties.

Our goal in this study was to evaluate multiagent intravesical therapy to induce remission of the disease in patients who did not respond to previous single-agent therapy.

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Patients and methods

Between September 19, 1987, and February 19, 1991, 25 patients (24 women and 1 man) meeting the criteria for IC (Tables 1, 2) were treated by the protocol outlined below. The average age of the patients was 50 years (range, 35–69 years). The duration of symptoms before diagnosis ranged from 1 to 17 years (mean, 7.2 years). All patients had previously received intravesical treatment with one of the following agents: silver nitrate, DMSO, or chloropactin. Exception to the NIDDK (National Institute of Diabetes and Digestive and Kidney Disease) criteria was given to two patients who demonstrated urodynamic evidence of bladder instability. These two patients responded poorly to traditional anticholinergic therapy. Five patients who had histories of only mild urinary incontinence were included.

Our treatment protocol was utilized (Fig. 1), since all patients came to our clinic on a referral basis. Although all patients had previously been diagnosed with IC, they were reevaluated to exclude other urologic pathology. Hydrodistension and cystoscopy using general anesthesia were also performed.

Following initial cystoscopy, the bladder was filled to capacity with sterile saline at 80 cmH_2O for 3 min. The bladder was then drained and cystoscopy was repeated. Bladder biopsies were taken from the lateral bladder walls and the bladder base by use of cold-cup biopsy forceps. Suspicious lesions were also biopsied. With the patient still under anesthesia, a premixed solution of 50 ml of 50% DMSO, 40 mg of methylprednisolone (Soul-Medrol), and 5000 units of heparin sulfate was instilled into the bladder. Patients who showed no cystoscopic sign of IC underwent further examination, which included consultation with a gynecologist, a psychiatrist, and a neurologist. If another pathology was found to be the cause of the symptoms, it was treated according to the cause and that patient was excluded from the study.

The patients who were selected for the study came to the office and received treatment weekly for another 5 weeks. Those who experienced immediate bladder spasms were premedicated with belladonna and opium rectal suppositories. Several of these patients who experienced severe sensitivity to catheterization were premedicated by the application of 2% lidocaine hydrochloride intraurethrally before the instillation. If a relapse of the symptoms was experienced, the patient received another course of instillation, depending on the severity of the symptoms. One to two instillations per month for 3 months were usually enough to induce another remission. A short remission or the persistence of symptoms was an indication to supplement the previous treatment with medications, including anticholinergics and/or amitryptiline. Patients who achieved a clinical remission were evaluated every 3–6 months. In case of a relapse, a repeat multiagent instillation was performed.

In patients in whom the irritative symptoms persisted after completion of the initial therapy, ancillary treatment was instituted (Fig. 1). Patients who showed only a partial response, if any, to the initital therapy received additional oral pharmacotherapy. If this treatment brought inadequate relief, transvaginal stimulation (TVS) was carried out. Only those patients who failed to respond to all conservative therapies were evaluated for surgical intervention (Fig. 1).

For clinic visits by IC patients, we designated a larger time block because the continued education and support of both the patient and the partner were critical in gaining the patient's acceptance of the long-term treatment protocol. All patients were encouraged to attend the meeting of the local chapter of the IC support group.

Results

On the present protocol, 23 of 25 patients (92%) achieved an initial remission for an average of 8.1 months. In all, 9 patients (36%) had 1 or more relapses. However, all achieved a subsequent remission lasting an average of 8.0 months. A total of 12 patients required supplemental oral medications: amitriptyline in 6 patients, oxybutynine in 3 patients, and imipramine in another 3 patients. Significantly, no patient experienced generalized effects from the instillations. Of the two patients not responding to the protocol, one never experienced a complete resolution of her symptoms and was sent to the pain clinic, where sacral blocks were performed with good results; the other patient showed a bladder capacity of 180 ml under anesthesia and urodynamically had a low bladder compliance (end-stage bladder).

The patients were divided into two groups according to their bladder capacity (Table 3). A total of 20 patients (80%) in group I had a normal capacity under anesthesia. Cystometrograms showed a decreased volume at first urge, a decreased functional (awake) capacity, and a normal bladder compliance. In all, 5 patients (20%) in group II were found to have a decreased bladder capacity while

Table 1. Criteria for inclusion as IC

Automatic inclusions:
Hunner's ulcer
One of the following two criteria must be present:
1. The presence of glomerulations on cystoscopic examination
a) The glomerulations must be diffuse, i.e., they must be present in the three quadrants of the bladder and there must be at least ten glomerulations per quadarant
b) The examination for glomerulations will occur after distention of the bladder to 80–100 cmH_2O per 1–2 min with the patient under anesthesia
c) The glomerulations to be considered must not be along the path of the cystoscope
2. The presence of a classic Hunner's ulcer on cystoscopic examination
One of the following two criteria must be present:
a) Pain associated with the bladder
b) Urinary urgency
Positive factors:
Pain on bladder filling relieved by emptying
Pain (suprapubic, pelvic, urethral, vaginal, or perineal)
Glomerulations on endoscopy
Decreased compliance on cystometrogram

Table 2. Criteria for exclusion as IC

Automatic exclusions:
Age <18 years
Benign or malignant bladder tumors
Radiation cystitis
Tuberculous cystitis
Bacterial cystitis
Vaginitis
Cyclophosphamide cystitis
Symptomatic urethral diverticulum
Uterine, cervical, vaginal, or urethral cancer
Active herpes
Bladder or lower ureteral calculi
Waking frequency, <5 times in 12 h
Nocturia, <2 times
Symptoms relieved by antibiotics, urinary antiseptics, urinary analgesics (e.g., phenazopyridine hydrochloride)
Duration, <12 months
Involuntary bladder contractions (urodynamics)
Capacity, >400 cc; absence of sensory urgency

Adopted from the NIDDK workshop on interstitial cystitis held at Bethesda, Maryland, on August 28–29 1987

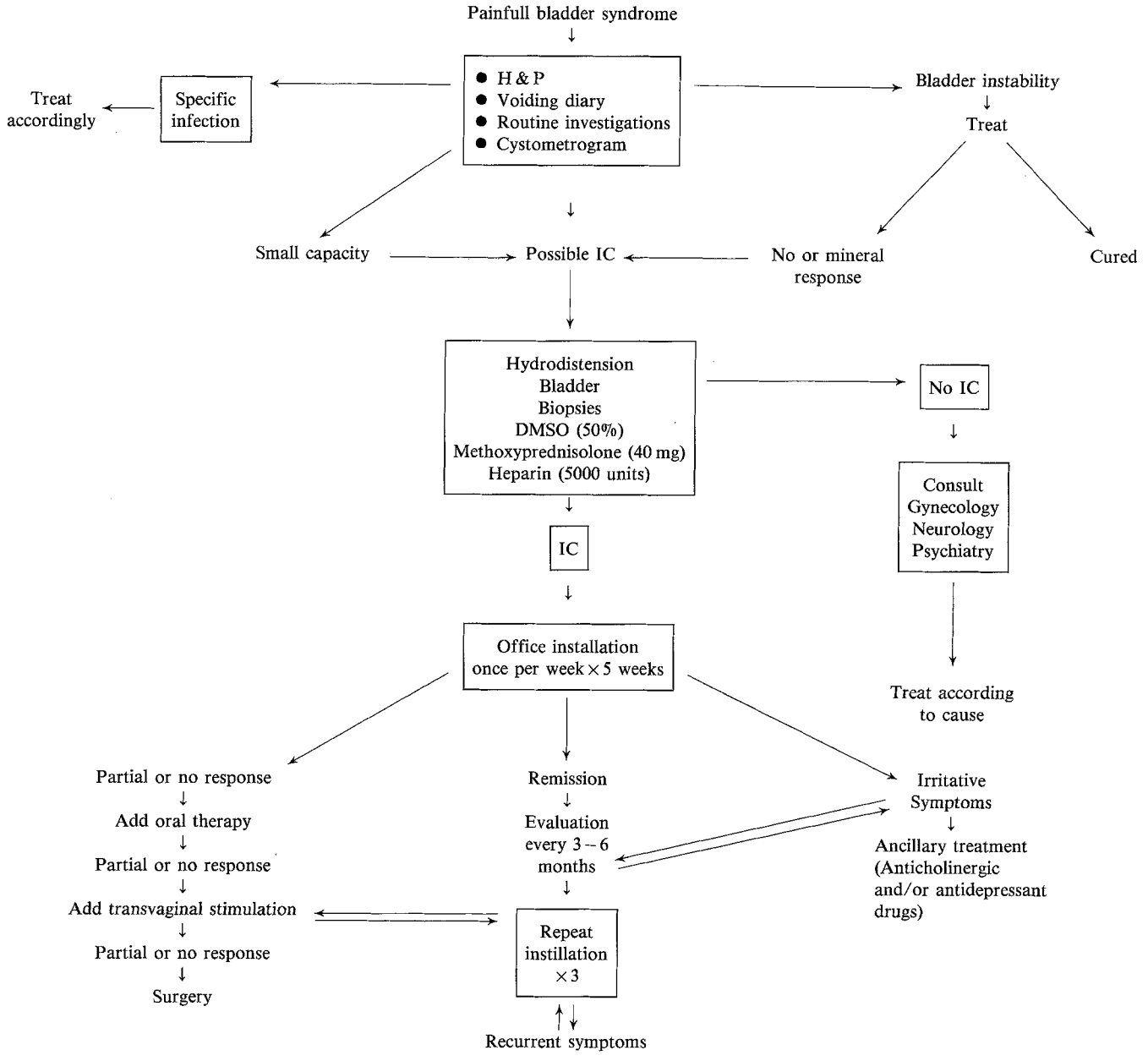

Fig. 1. Flow chart for the management of IC patients

both awake and under anesthesia. Additional urodynamic findings showed five patients with mild stress urinary incontinence, two patients with detrusor instability, and one patient with an areflexic bladder (also described as detrusor myopathy) [26].

Patients in group I had an average bladder capacity of 351.2 ml while awake and 699.4 ml while under anesthesia. This difference represents a significant 99.6% change ($P<0.001$). In group II, the percentage of change in the bladder capacity while awake (137 ml) in relation to the average bladder capacity under anesthesia (164 ml) was only 19.6% ($P<0.001$). Cystoscopically, all patients in both groups showed glomerulations. Hunner's ulcers were present in 60% of the group II patients but were seen in only 5% of the group I patients.

Histopathological examination showed that inflammatory changes were more frequent (100%), severe, and pronounced in group II as compared with group I. Mast-cell hyperplasia was present in all patients (100%) in group II but was noted in only 61% of the group I patients (Table 4).

In summary, our protocol of multiagent intravescial instillation supplemented by oral pharmacotherapy and intensive supportive therapy indicates that many IC patients are capable of achieving significant control of their symptoms and improving the quality of their lives. A

Table 3. Urodynamic findings in patients with IC

	Group I	Group II	*P* value
Number of patients	20 (80%)	5 (20%)	
Age (average)	48.2 years	59.8 years	
Bladder capacity (awake, ml)	351.2±18.7	137 ±11.7	<0.001
Bladder capacity (anesthetic, ml)	699.4±26.4	164 ±12.8	<0.001
% Change in bladder capacity	99.1	19.6	
Bladder compliance (ml/cmH_2O)	52.4±7.2	51.3 ±16.2	Not significant
Incontinence (SUI)	5	0	
Detrusor instability (DI)	2	0	
Areflexic bladder	1	0	

Table 4. Pathological findings in patients with IC

	Group I	Group II
Glomerulations	18[a] (100%)	5 (100%)
Hunner's ulcer	1/18 (5.56%)	3/5 (60%)
Histopathology:		
Mast cells[b]:		
Absent	5/13 (38.46%)	0
Mild to moderate	8/13 (61.54%)	4/5 (80%)
Severe	0/13 (0)	1/5 (20%)
Inflammatory changes	15/18 (83.3%)	5/5 (100%)
No inflammation	3/18 (16.7%)	0

[a] Biopies were not done for two patients in group I

[b] Giemsa stain studies were done for 13 patients in group I and 5 patients in group III

small but significant number of patients, however, will require alternative, more aggressive treatment measures.

Discussion

DMSO is the only agent approved by the Food and Drug Administration (FDA) for intravesical instillation in patients with IC. Its unmatched, long-term success (up to a 70% success rate) is attributed to its anti-inflammatory, analgesic, and muscle-relaxing properites [27, 28]. Unlike some intravescial agents, DMSO instillations do not require anesthesia and are not contraindicated in patients with vesicoureteral reflux. Local side effects such as transient bladder irritation and garlic-odor breath are relatively minor.

The potential benefits provided by heparin sulfate are attributable to its anti-inflammatory properties, including the inhibition of angiogenesis and fibroblast proliferation [24, 25]. Its ability to form a hydrophobic "protective barrier" layer on the mucosal surface is a potential benefit as well. Using it intravesically results in minimal absorption and avoids the potential systemic side effects seen on its parental administration. The potential benefit of prednisolone stems from its strong anti-inflammatory properties as well. Its penetration into the deeper layers of the bladder is enhanced by DMSO.

By using a combination of three agents, we obtained relief for patients who had not responded to single-agent therapy. Although the present investigation was not a randomized study, most of these patients responded favorably to the regimen and are leading a normal life.

Our results show two distinct groups of IC. Diagnosis of patients with a small bladder capacity, Hunner's ulcers, and severe symptoms could be straightforward, as in group II. On the contrary, the inclusion or exclusion of patients with a normal bladder capacity, even in the presence of severe symptoms, is usually physician-dependent, as in group I. We found no overlap between the two groups, nor did any of the patients with a small bladder capacity showed gradual progression of the disease. Careful review of our patients' records revealed that their symptoms started with a small bladder capacity. These findings lead us to believe that probably there are two types of IC patient.

Consideration of supratrigonal augmentation cystoplasty or even cystourethrectomy and ileal loop diversion should be reserved for the few patients with long-standing disease, severe symptoms, and a small bladder capacity who have not responded to other forms of therapy [29–31]. Our study suggests that multiagent intravesical therapy offers an effective and nonsurgical treatment to induce remission of IC.

References

1. Campbell A, Converse PE, Rodgers WL (1976) The quality of American life; perception, evaluations and satisfactions. Russell Sage Foundation, New York, pp 528–556
2. Oravisto KJ (1975) Epidemiology of interstitial cystistis. Ann Chir Gynaecol 172:75–77
3. Hunner GL (1915) A rare type of bladder ulcer in women: report of cases. Boston Med Surg J 172:660–664
4. Hanash KA, Pool TL (1970) Interstitial and hemorrhagic cystitis: viral, bacterial and fungal studies. J Urol 104:705–706
5. Clemmensen O, Lose G, Holm-Bentzen M, Colstrup H (1988) Skin reactions to urine in patients with interstitial cytitis. Urology 32:17–20
6. Oravisto KJ, Alfthan OS, Jokinen EJ (1970) Interstitial cystitis, clinical and immunological findings. Scand J Urol Nephrol 4:37–42
7. Silk MR (1970) Bladder antibodies in interstitial cystistis. J Urol 103:397–309
8. Bohne AW, Hodson JM, Rebuck JW, Reinhard RE (1962) An abnormal leukocyte response in interstitial cystitis. J Urol 88:387–391
9. Jokinen EJ, Alfthan Os, Oravisto KJ (1972) Antitissue antibodies in interstitial cystitis. Clin Exp Immunol 11:333–339
10. Phillips JI (1981) Inflammatory plasma cell infiltration of the urinary bladder in the aging C57BL lerfa mouse. Invest Urol 19:75–78
11. Mattila J, Harmoinen A, Hallstrom O (1983) Serum immunoglobulin and complement alterations in interstitial cystitis. Eur Urol 9:350–352
12. Hellstrom HR, Davis BK, Shonnard JW (1979) Eosinophilic cystitis, a study of 16 cases. Am J Clin Pathol 72:777–784
13. McGuire EJ, Lytton B, Cornog JL (1973) Interstitial cystitis following colocystoplasty. Urology 2:28–29
14. Mattila J (1982) Vascular immunopathology in interstitial cystitis. Clin Immunol Immunopathol 23:648–655

15. Mattila J, Pitkanen R, Vaalasti T, Seppanen J (1983) Fine-structural evidence for vascular injury in patients with interstitial cystitis. Virchows Arch 398:347–355
16. Larsen S, Thompson SA, Hald T, Barnard RJ, Giplin CJ, Dixon JS, Gosling JA (1982) Mast cells in interstitial cystitis. Br J Urol 54: 283–286
17. Dixon JS, Hald T (1986) Morphological studies of the bladder wall in interstitital cystitis. In: George NJR, Gosling JA (eds) Sensory disorders of the bladder and urethra. Springer, Berlin Heidelberg New York, pp 63–70
18. Simmons JL, Bunce PL (1958) On the use of an antihistamine in the treatment of interstitial cystitis. Am Surg 24:664
19. Clark IM (1981) Amitriptyline and perphenazine (Triptafeln, DA) in chronic pain. Anesthesia 36:210–212
20. Duthie AM (1971) The use of phenothiazines and tricyclic antidepressants in the treatment of intractable pain: S Afr Med J 51:246–247
21. Parsons CL, Stauffer C, Schmidt JD (1980) Bladder-surfac glycosaminoglycans: an efficient mechanism of environmental adaptation. Science 208:605
22. Parsons CL, Schmidt JD, Pollen JJ (1983) Successful treatment of interstitial cystitis with sodium pentosanpolysulfate. J Urol 130:51–53
23. Sant GR, Ucci AA, Alroy J (1986) Bladder surface glycosaminoglycans in interstitial cystitis. J Urol 135:175A
24. Lose G, Frandsen B, Hojensgard JC, Jespersan J, Astrup T (1983) Chronic interstitial cystitis. Increased levels of eosinophil cationic protein in serum and urine and an ameliorating effect of subcutaneous heparin. Scand J Urol Nephrol 17:159–161
25. Lose G, Jepersen J, Frandsen B, Hojensgrad JC, Astrup T (1985) Subcutaneous heparin in the treatment of interstitial cystitis. Scand J Urol Nephrol 19:27–29
26. Hirsch LB, Montella JM, Bent AE (1991) Detrusor instability. In: Ostergard DR, Bent AE (eds) Urogynecology and urodynamics theory and practice, 3rd edn. Williams and Wilkins, Baltimore, pp 363–367
27. Stewart BH, Shirley SW (1976) Further experience with intravesical dimethyl sulfoxide in treatment of interstitial cystitis. J Urol 116:36–38
28. Fowler JE JR (1981) Prospective study of intravesical dimethyl sulfoxide in treatment of suspected early interstitial cystitis. Urology 18:21–26
29. Worth PHL, Turner-Warwick R (1973) The treatment of interstitial cystitis by cystolysis with observations on cystoplasty. Br J Urol 45:65–71
30. Weiss JP, Wein AJ, Hanno PM (1984) Sigmoidocystoplasty to augment bladder capacity. Surg Gynecol Obstat 159:377–380
31. Seddon JM, Best L, Bruce AW (1977) Intestinocystoplasty in treatment of interstitial cystitis. Urology 10:431–435