

A PILOT OPEN LABEL STUDY OF CYSTOPROTEK® IN INTERSTITIAL CYSTITIST.C. THEOHARIDES¹ and G.R. SANT²

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Interstitial cystitis (IC) is a disorder of the urinary bladder characterized by urgency, frequency, nocturia and suprapubic pain. IC occurs primarily in women and symptoms are exacerbated by stress, ovulatory hormones and certain foods. IC pathogenesis is unknown, but the most consistent findings involve some dysfunction of the bladder glycosaminoglycan (GAG) protective layer and a high number of activated bladder mast cells. There is no effective therapy even through intravesical administration of dimethylsulfoxide (DMSO) or oral pentosanpolysulfate (PPS) have had variable success. A dietary supplement, CystoProtek®, was formulated with the natural GAG components chondroitin sulfate and sodium hyaluronate to provide urothelial cytoprotection, together with the flavonoid quercetin that has anti-inflammatory properties and inhibits activation of mast cells. Thirty-seven female patients diagnosed by the NIDDK criteria who had failed all forms of therapy took six softgel CystoProtek® capsules per day for 6 months. Global assessment scale was reduced from 9.0 ± 2.9 to 4.3 ± 2.1 ($p < 0.05$); moreover, the O'Leary/Sant Symptom Index decreased from 16.3 ± 3.1 to 6.9 ± 4.2 ($p < 0.05$) and the Problem Index from 13.1 ± 3.7 to 5.4 ± 4.0 ($p < 0.05$). These results are very promising and warrant a larger study that may permit further analyses with respect to other, especially atopic, comorbid diseases.

Interstitial cystitis (IC) is a bladder syndrome that occurs mostly in women with symptoms of urinary urgency, frequency, nocturia and suprapubic/pelvic pain (1). IC occurs also in males and recent evidence suggests that chronic non-bacterial prostatitis and prostatodynia may be a similar condition. The prevalence of IC from population-based data from the US Nurses' Health Study I and II was estimated at about 60 cases/100,000 women. Recent publications have suggested that the NIDDK criteria may be too restrictive and the term IC/chronic pelvic pain syndrome (CPPS) has been adopted to indicate the broad area affected and to include more patients.

IC patients appear to be young and middle-aged women, (1) but adolescents and children are also affected. The symptoms worsen periodically

and common triggers include psychological or physical stress (2). In 75% of women, sexual intercourse appears to exacerbate their symptoms (3). Almost 60% of IC patients have symptoms or history of atopic disease and over 30% have concurrent diagnosis of irritable bowel syndrome (IBS) (4). It was also recently shown that IC and panic disorder may be genetically linked, possible through mast cell activation. In view of such findings, IC has been considered a neuroimmunoendocrine condition (3).

Diagnosis of IC is usually based on a history of irritative voiding symptoms (urgency, frequency), pain and negative urine cultures (5). The more common, non-ulcer, variety is found in almost 90% of IC patients and is characterized by petechial bladder mucosal hemorrhages ("glomerulations")

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without ulceration. However, recent papers have shown that glomerulations may occur in non-IC patients and they do not correlate with the degree of inflammation; in fact, patients with nonulcer disease may have minimal evidence of bladder inflammation, while those with inflammation present with more pronounced symptoms (6). In those patients with bladder inflammation, the urine had increased levels of IL-6, while the bladder wall contained an increased number of mast cells (7), many of which were positive for IL-6 and/or stem cell factor (SCF) receptor (c-kit) and had increased expression of intercellular adhesion molecule-1 (ICAM-1) (8). These findings, along with some defect in the protective glycosaminoglycan (GAG) layer of the bladder (9) constitute the main pathologic features.

A dietary supplement was formulated to include natural molecules that could replenish the GAG and reduce inflammation. This formulation, CystoProtek[®] was used in female patients who had failed other forms of treatment.

MATERIALS AND METHODS

The ingredients and their sources in CystoProtek[®] are listed in Table I. Patients 18 years or older were selected using the criteria established (5) for research studies by the USA National Institutes of Health (NIH) and include: (a) positive medical history of urinary urgency and pain for at least six months, urinary frequency >8 times per day while awake and >2 times during the night, (b) negative urine cultures, (c) cystoscopic evidence of ulcers or mucosal hemorrhages (glomerulations) during bladder hydrodistention under general or spinal anesthesia, and bladder biopsy in order to exclude other bladder pathology, such as tuberculosis or transitional carcinoma.

Patients were excluded if (a) any urinary tract or prostatic infection within 3 months prior to the study or any active genital infection, (b) history of cyclophosphamide, chemical or radiation cystitis, (c) history of bladder tumors or tuberculosis, and (d) if they had hydrodistention, intravesical therapy or had been treated with pentosan polysulfate sodium (Elmiron[™]) during the last 3 months prior to starting CystoProtek[®]. Otherwise, patients were allowed to remain on any other medication they may have been using routinely for either pain or any other concurrent medical condition, except for any opioid analgesic.

The mean age of the 37 female patients enrolled was 39.4 ± 4.1 and the duration of IC symptoms was 5.1 ± 3.2 /years. Patients took two softgel CystoProtek[®] capsules 3 times per day with some food for six months. IC symptoms were evaluated using a global symptom visual scale (0 = least, 10 = worst) and the validated Symptom and Problem Scoring index by O'Leary and Sant (10) at the beginning and at the end of the treatment period. Differences were evaluated using the non-parametric Mann-Whitney U test. Significance was denoted by $p < 0.05$.

RESULTS

The demographics of the 37 female patients are shown on Table I. The mean age was 39.4 ± 4.1 years with symptom duration 5.1 ± 3.2 years (Table II). Other concurrent medical problems included allergies (59%), endometriosis (20%), fibromyalgia (20%), irritable bowel syndrome (30%), migraines (10%) and vulvodynia (15%).

The global assessment at the beginning of the treatment period was 9.0 ± 2.9 and decreased (52.2%) to 4.3 ± 2.1 ($p < 0.05$) at the end (Table III). Similarly, the O'Leary/Sant IC Symptom Index (0-20) decreased from 16.3 ± 3.1 to 6.9 ± 4.2 ($p < 0.05$) and the Problem Index (0-16) decreased from 13.1 ± 3.7 to 5.4 ± 4.0 ($p < 0.05$).

There were no side effects except some transient "oil taste coming up" and stomach upset in 9/37 patients, especially those who had a history of gastritis or acid reflux. This minor problem disappeared if patients took some antacid or froze the softgel capsules before swallowing to decrease dissolution in the stomach.

DISCUSSION

This is the first report of a dietary supplement specifically formulated, based on scientific publications, to help replenish the bladder lining and reduce inflammation using natural ingredients. The results show >60% benefit in patients who had failed all other forms of therapy. The treatment of IC presents a unique challenge for clinicians since the pathogenesis of the disease is not known and is very likely to be multifactorial in origin (11). The prevailing premises are: (a) altered bladder permeability as evidenced by damaged bladder protective GAG layer, (b) an increase in

Ingredients	Amount per capsule	Source	Purity	Country of origin
Glucosamine sulfate	130 mg	Shell fish chitin	>99%	China
Chondroitin sulfate	150 mg	Shark cartilage	>90%	China
Sodium hyaluronate	20 mg	Chicken combs	>98%	Japan
Quercetin dihydrate	150 mg	Saphora plant	>99%	China
Olive kernel extract	448 mg	Olive seeds	100%	Greece

Table I. *CystoProtek*[®] ingredients and sources.

This formulation in softgel capsules is made by Tischcon Corp. (Westbury, NY), an FDA certified GMP facility. All ingredients are free from any bovine products or preservatives. The softgel is made of porcine gelatin.

Parameter Category	Results
Age⁺	Years
Mean ± SD	39.4 ± 4.1
Symptom duration	
Mean ± SD	5.1 ± 3.2
Other concurrent medical problems	Percent
Allergies	59
Endometriosis	20
Fibromyalgia	20
Irritable bowel syndrome	30
Migraines	10
Vulvodynia	15
Other	5

Table II. *Demographic and baseline characteristics of enrolled patients.*

⁺Female Caucasian (n=39).

the numbers and especially activation of bladder mast cells, possibly secondary to sensory nerve sensitization and tachykinin release. The goal of treatment is to control or reduce symptoms, while providing logistic support.

The most commonly reported therapeutic modalities, as recently tabulated by the Interstitial Cystitis Data Base, were cystoscopy with hydrodistention, oral amitriptyline and intravesical heparin (12). The passive bladder hydrodistention at the time of diagnostic cystoscopy provides temporary (usually 1-2 months) symptomatic relief in about 25% of IC patients and may be repeated 2-3 times (12). This procedure may be followed by intravesical dimethylsulfoxide (DMSO) administration.

A defective bladder GAG layer, leading to a “leaky” bladder epithelium (9), has been one of the most enduring pathogenic explanations for IC.

The GAG layer is composed primarily of chondroitin sulfate and sodium hyaluronate, with glucosamine sulfate serving as the synthetic building block. It is, therefore, of interest that urine hyaluronic acid was higher in IC patients, as compared to controls, indicating loss of this protective molecule (13). Moreover, total urine glycosaminoglycans, including chondroitin sulfate, were also decreased in the urine of IC patients, even though they normalized to creatinine. There is also recent evidence that exposed bladder epithelial cells from patients with IC produce an inhibitor of heparin-binding epidermal growth factor, thus preventing urothelial cell proliferation; this factor was recently identified as a member of the Frizzled family of surface proteins.

PPS was the only oral drug approved by the US Food and Drug Administration under the Orphan Disease Act on findings that it could “replenish”

Table III. Effect of CystoProtek® on IC symptoms.

Response (n = 39)	Before	After
Global Assessment	9.0 ± 2.9 ⁺	4.3 ± 2.1 [*]
O'Leary/Sant IC Symptom Index (0-20)	16.3 ± 3.1	6.9 ± 4.2 [*]
O'Leary/Sant IC Problem Index (0-16)	13.1 ± 3.7	5.4 ± 4.0 [*]

⁺Mean ± SD^{*}p < 0.01**Table IV.** Effect of olive kernel extract (OKE) on absorption of chondroitin sulfate in rats.

Preparation	n	Absorption (%)
- OKE	5	3.9 ± 1.2
+ OKE	3	14.3 ± 2.9 [*]

⁺Chondroitin sulfate was tritiated (³H) at New England Nuclear (specific activity = 4.3 mCi/ml); 2.5 mCi ³H-chondroitin sulfate was given orally to rats with or without mixing in OKE; plasma radioactivity was measure 8 hr later using a beta-counter.

^{*}p < 0.05

the GAG layer, but a recent multicenter clinical trial sponsored by the US National Institutes of Health (NIH) showed that it had no effect in moderate to severe IC (14). The beneficial effect of the glycosaminoglycans may also derive from inhibition of bladder mast cell activation, since both PPS (15) and chondroitin sulfate were (16) shown to inhibit mast cell activation amply documented in IC bladders (3).

Chondroitin sulfate was included in CystoProtek® because it is one of the most common natural proteoglycans. It is a surface recognition site and a major component of human mast cell secretory granules. Chondroitin sulfate has been used, together with its building block glucosamine, for the treatment of osteoarthritis, with potential benefit as indicated by a recent meta-analysis. Moreover, preincubation of rat peritoneal mast cells for 10 min with chondroitin sulfate resulted in 76.5% inhibition of histamine release (p=0.0004) (16). In contrast, the inhibitory action of the "mast cell stabilizer" drug cromolyn decreased rapidly if preincubation lasted for more than 1 min

(16). The inhibitory effect of chondroitin sulfate extended to stimulation of mast cells by the neuropeptide SP, as well as by immunoglobulin E and anti-IgE, and was correlated with its inhibitory effect on intracellular calcium ion levels. A recent publication showed that there was no cross-reactivity between sensitivity to sulfonamide antibiotics and other sulfate containing products (17).

There are many chondroitin sulfate preparations available for arthritis, but, unfortunately there are a number of problems with those: (a) there is no standardization in their content of chondroitin sulfate which can vary significantly in the size and degree of sulfation (the bigger and more sulfated the better); (b) the absorbance is extremely low (<5%) making it difficult to achieve therapeutic levels; and (c) the most common source is cow's trachea with its inherent risk of spongiform encephalopathy ("mad cow disease"). To avoid these problems, CystoProtek® uses chondroitin sulfate from shark cartilage mixed with olive kernel extract (OKE); this patented formulation improves its absorption considerably (Table IV). Moreover, olive oil is, itself, rich in bioflavonoids and has many cytoprotective properties (19).

CystoProtek® also contains sodium hyaluronate, another natural proteoglycan found in the GAG layer, in connective tissue and in human mast cell secretory granules. Sterile sodium hyaluronate preparations have been used as a device to replenish joint viscosity by intra-articular injection, especially in osteoarthritis. A recent publication also reported increased urine hyaluronic acid in IC patients. Sodium hyaluronate (0.04%) instilled intravesically weekly for 4 weeks, followed by monthly administration resulted in 70% of patients with complete or partial symptom reduction, but the response decreased after 6 months (20), and its effect varied considerably.

Rats pretreated intravesically with a 0.4% sodium hyaluronate for 30 min prior to acute immobilization stress had significant inhibition of bladder mast cell activation, as well as mast cell protease I and IL-6 secretion (21). This effect could be mediated through CD44 which is expressed on mast cell surface and binds hyaluronic acid.

Quercetin was added to CystoProtek® because it inhibits mast cell secretion (22,23) and proliferation, including allergic stimulation of human mast cells. Quercetin also inhibits mucosal mast cells, while the “mast cell stabilizer” cromolyn does not (23,24). Quercetin belongs to a unique class of natural compounds, the flavonoids that are present in plants, and seeds; they have potent anti-oxidant, cytoprotective and anti-inflammatory activities. Quercetin specifically inhibits mast cell secretion of IL-6 (25), which has been shown to be increased in IC urine, and is a potent inflammatory cytokine. The mechanism of action of quercetin depends on a particular pattern of hydroxylation of its B ring (22). The combination of the flavonoid quercetin with the proteoglycan chondroitin sulfate was shown to have additive mast cell inhibitory activity (25).

Another preparation containing quercetin was also reported to have benefit in IC. However, that preparation evidently contains a number of other ingredients which are not disclosed, as are not the amounts or their sources. Moreover, the most common source of quercetin in products other than CystoProtek® is from faba beans, ingestion of which could cause hemolytic anemia in those individuals (many of Mediterranean origin) who have glucose-6-phosphate dehydrogenase (G₆PD) deficiency. Unfortunately, these facts are not available to the unsuspecting consumer (25).

In conclusion, effective treatment for IC has been hampered by the lack of definitive pathogenesis frustrating both patients and physicians. The formulation tested in this study constitutes a new concept in the treatment of IC, in that it uses a multi-modality approach of molecules, the mechanisms of action of which allows them to act at different points in the suspected pathogenic pathways in the bladder. Patients with documented bladder mastocytosis (7) and/or a history of allergies, may get even greater benefit with a combination of CystoProtek® and Hydroxyzine (28). Hydroxyzine, in addition to its well-known

histamine-1 receptor antagonist/actions, also inhibits mast cell activation and neurogenic bladder inflammation (29). Moreover, it is a weak anxiolytic and may help in those individuals where stress is known to exacerbate IC symptoms possibly through mast cell activation (30).

The present results with CystoProtek® constitute the first oral multimodal therapy based on published scientific evidence to deliver synergistic effects and warrant a larger trial.

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