The Effectiveness of Calcium Glycerophosphate in Decreasing Symptoms of Interstitial Cystitis and Improving Quality of Life of Patients with Food-related Exacerbations

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Introduction

Interstitial cystitis (IC) defined as urinary urgency, frequency, and pelvic pain encompassed a spectrum of severity from mild irritating symptoms to an incapacitating disease. The typical onset is in youth or middle age with a heavy female predominance (90%). The prevalence of IC has been reported to be anywhere from 30/100,000 to 500/100,000 of the total population, or as many as 1 million Americans. This syndrome represents a spectrum of bladder dysfunction or voiding complaints, including bladder and/or pelvic pain, urgency, frequency, nocturia and dysuria, while the urine culture remains sterile. Today, despite improved diagnostic modalities, IC remains a diagnosis of exclusion. While the etiology of IC is currently unknown, most authors believe it to be multifactorial. Etiologic theories include infection, mast cell involvement, increased bladder epithelial permeability, autoimmunity or allergy, urine toxicities and neurogenic mechanisms.

The typical course of IC is chronic and non-progressing, characterized by symptom flares and remissions. Once the diagnosis is confirmed, treatment is aimed at alleviating symptoms and modifying exacerbating factors, such as stress, intercourse and certain foods. Several studies have shown the relationship between acid-urine-producing foods or liquids and an increase in painful bladder symptoms, as well as the alleviation of these symptoms with restriction of foods. The most commonly cited foods and beverages are coffee, chocolate, alcohol and carbonated drinks, citrus fruits, and tomato-based products. While all of the studies to date have focused on the elimination of these foods,

no study has looked at the efficacy of alleviating symptoms without removing these foods from the diet of IC patients. Calcium glycerophosphate has been shown to reduce the titratable acid in the aforementioned foods by 50-100%. In this study, we report our results on the efficacy of calcium glycerophosphate in reducing the symptoms of IC aggravated by food and improving patients overall quality of life.

Abstract

OBJECTIVE: We sought to evaluate patients with diagnosed Interstitial Cystitis (IC) and associated food exacerbations to assess the effectiveness of calcium glycerophosphate on improving symptoms and quality of life. **METHODS:** 379 patients diagnosed with IC by their urologist were included in this prospective nonrandomized study. Prior to treatment, each patient completed a four-week food diary to confirm exacerbation of symptoms, an O'Leary-Sant questionnaire to confirm severity of symptoms, and SF12 quality of life survey. Patients were then asked to take 2 tablets (0.66g) of calcium glycerophosphate prior to each daily meal for four weeks and complete the above surveys again after the 4-week period. The specific foods evaluated were: pizza, coffee, carbonated drinks, alcohol, acidic fruits and juices, tomato-based products, chocolate, and spicy foods. Post-treatment evaluation was performed with the McNemar's test comparing symptom reduction versus exacerbation. Pain, discomfort, and urgency were evaluated on a 10-point severity scale and compared using the signed-rank test. **RESULTS:** 203 patients completed the follow-up survey for a response rate of 53.6%. Analysis of attrition demonstrated no difference between participants and non-participants regarding age, severity of symptoms, and associated conditions. A decrease in symptom severity was seen in greater than 40% of responders with exacerbations related to pizza, coffee, acidic fruits and juices, spicy foods, and tomato-based products. A 20%-30% reduction was seen in responders with exacerbations related to carbonated drinks, alcohol, and chocolate. Pain and discomfort decreased from 5.3 to 3.6 ($p<.0001$), while urgency was reduced from 5.3 to 4.1 ($p<.001$). Regarding quality of life issues the majority of responders had a positive change or no change ($p<.0001$). **CONCLUSIONS:** Calcium glycerophosphate appears to reduce IC symptoms in patients with food-related exacerbations and improve their quality of life.

Materials and Methods

Patients for this prospective nonrandomized study were identified from a large outpatient urology practice and demographic characteristics were obtained. Prior to treatment, each patient completed a 4-week food diary to confirm exacerbation of symptoms, an O'Leary-Sant questionnaire to confirm severity of symptoms, and the SF12 quality of life survey. Patients were then instructed to ingest 2 tablets (0.66g) of calcium glycerophosphate prior to each daily meal for 4 weeks. A food diary for specific foods, such as pizza, coffee, carbonated drinks, alcohol, acidic fruits and juices, tomato-based products, chocolate, and spicy foods, was conducted during the 4-week treatment period. Post-treatment evaluation was performed with the McNemar's test (a paired chi-square test) comparing the proportion of participants reporting symptom reduction versus those reporting symptom exacerbation. This analysis was restricted to those participants who indicated consuming the specific foods during the study period. The change in risk due to use of CGP is reported as an odds ratio (OR) with an associated 95% confidence interval and level of significance. The odds ratio describes the proportional increase or decrease in IC symptoms relating to the use of CGP. An O'Leary-Sant questionnaire and SF12 were also repeated after treatment. Pain, discomfort, and urgency were evaluated on a 10-point severity scale and compared using the signed-rank test. Quality of life issues were evaluated on a 4-point severity scale and also compared using the signed rank test.

Results

Demographics

A total of 379 individuals participated in the study. The sample was predominantly female (94%), Caucasian (97%), and above the age of 50 (59%). About one-third of participants reported having symptoms of IC for less than 5 years, while roughly one-third reported having symptoms for more than 15 years. About 62% of participants reported bladder pain and discomfort as the predominant symptom and 94% of the group has sought treatment for their symptoms. Among co-existing conditions, medication allergies were most common (55.1%), followed by allergic sinusitis (34%), and food allergy (30.6%).

Analysis of attrition

Of the 379 individuals originally enrolled in the study, 203 (53.6%) completed the follow-up survey. Analysis of attrition revealed that participants and non-participants were not statistically different in terms of age, gender, and race. Participants and non-participants were also comparable on symptoms relating to IC. Approximately 60% of participants and non-participants reported pain as the predominant symptom, and, while responders reported urgency as the second most common symptom (22.1%), non-responders reported frequency of urination as the second most common symptom (21.2%). These differences were not large enough to achieve statistical significance. Participants and non-participants did differ in 2 areas on the IC symptom index and IC

problem index. Participants arose more frequently at night to urinate ($p<=0.03$) and also found the need to urinate with little warning to be more problematic ($p<=0.08$) than non-participants. Finally, participants and non-participants were not statistically different as related to age of symptom onset, duration of symptoms, and occurrence of pre-existing conditions. Thus, although 46.4% of the total participant pool failed to complete the follow-up survey, attrition appears to be independent of the gross demographic characteristics, symptoms of IC, pre-existing conditions, or food-exacerbated symptoms. Based on these analyses, it would appear that patients completing both surveys are comparable to the total sample initially enrolled.

Effect of CGP on food-specific symptoms

Participants were questioned about exacerbation of IC symptoms while consuming certain foods in the 4 weeks prior to taking CGP, and again after taking the supplement for 4 weeks. Table 2 shows the proportion of study participants reporting symptoms before and after use of CGP. While the number of participants providing usable responses for each food varies substantially, there is a significant improvement in symptom severity for each food studied. A greater than 40% reduction in symptom severity was seen for pizza, coffee, acidic fruits and juices, and spicy foods, while a 15-40% reduction was seen for carbonated and alcoholic beverages, tomato-based products, and chocolate. It is also interesting to note that CGP appeared to reduce the number of foods that aggravated symptoms. Prior to using CGP, participants reported an average of 4.3 foods (of the 8 considered) that aggravated their IC symptoms. After using CGP for 4

weeks, the average number of foods that aggravated symptoms decreased to 1.7 ($p<0.001$). The survey suggests that CGP affords substantial reduction in IC symptoms among those participants reporting food-related exacerbations. The effect appears particularly pronounced for symptoms exacerbated by coffee, pizza, spicy foods, and acidic fruits and juices. CGP also appeared to reduce the average number of foods per person cited as aggravating symptoms.

General symptom evaluation before and after use of CGP

Participants rated bladder pain and discomfort as well as urinary urgency on a 10-point scale (0-9), where higher scores indicated increased symptom severity. In 179 respondents, the mean pain rating prior to using CGP was 5.3 (+/-2.2), whereas the mean pain rating after using CGP was 3.6 (+-2.0), ($p<0.0001$). When respondents were classified by their change in ratings (pre – post), 70.4% reported a reduction in pain and discomfort, while 20.7% indicated no change in symptoms, a significant reduction ($p<0.0001$) using the signed rank test. In 181 respondents, the mean urgency rating prior to using CGP was 5.3 (+-2.2), while the mean rating after using CGP was 4.1 (+-2.1), ($p<0.001$). When participants were classified by their change in ratings (pre – post), 61.3% reported a reduction in urgency, while 24.9% indicated no change in urgency scores before or after using CGP. This also represents a significant reduction ($p<0.001$) using the signed rank test.

Quality of life questionnaire

Respondents were asked to indicate the proportion of time that IC prevented them from participating in or performing various activities. The activities were rated on a 4-point scale with higher scores indicating that the condition substantially interrupted the activity. Results are summarized in Table 3. Overall, respondents indicated that there was improvement in quality of life measures, including mental attitude, ability to deal with stress, and ability to participate in social, interpersonal, and work-related activities. Although improvements were substantial, approximately half of those responding reported no change for many of the measures.

Discussion

The etiology of interstitial cystitis (IC) remains unclear. Current theories include a defective urothelium resulting from a quantitative deficiency of the bladder's surface coat of glycosaminoglycans (GAGs) (1). Parsons has demonstrated that the instillation of potassium chloride into the bladder can mimic the symptoms of IC and assist in its diagnosis, particularly in those patients with a urothelial abnormality (2). Other contributing factors to the symptoms of IC or bladder hypersensitivity may be associated bladder mastocytosis and an increase in mast cell activation (3). Bladder hypersensitivity may be related to the excitation of sensory nerves, especially small pain C-fibers that trigger an inflammatory process through the release of substance P and calcitonin gene-related peptides (4).

Many different foods have been implicated in promoting the symptoms of IC, most frequently, coffee, chocolate, carbonated beverages, alcohol, citrus, and tomatoes (5). Several authors have noted that most patients experience an improvement in their symptoms once the offending food is eliminated from their diet (6, Erickson, 7 Whitmore, 8 Gillespie). The mechanisms of symptom increase for these foods are unknown, but may be related to acid, potassium, or amine precursors (e.g. tyramine, tryptophan) (5, Gillespie). Although dietary management may offer a cost-effective approach to alleviating the food-related symptom exacerbations in IC patients, it may also leave the patient nutritionally depleted and their quality of life restricted. An effective method of treating the symptoms but leaving the diet intact would be an important tool in the arsenal

against IC.

Our study focused on 8 foods frequently noted to promote symptoms of IC: pizza, coffee, carbonated beverages, alcohol, acidic fruits and juices, tomato-based products, chocolate, and spicy foods. Calcium glycerophosphate has demonstrated that it reduces the titratable acidity in these foods by 50-100%. It is conceivable that, in the face of a defective bladder lining or increased activation of the unmyelinated C-fibers, a reduction in the acidity level can reduce the severity and frequency of IC symptoms in those patients noted to have food-associated symptoms. A greater than 40% reduction in symptoms was seen for pizza, coffee, acidic fruits and juices, and spicy foods, while a lower, but still significant, reduction was seen for the other foods. (Table 2) Overall a significant proportion of subjects noted an improvement in quality of life during the study. (Table 3)

We recognize that this study is limited because the population does not meet the strict NIDDK research criteria for interstitial cystitis and the subjects were selected based on their food associated exacerbations of their symptoms. Also, we recognize that this was not a double blinded randomized placebo controlled study. We attempted to perform such a study and had a very high attrition rate possible because patients easily identified that they were receiving placebo and the CGP is available over-the-counter. With respect to the limitations stated above, the results suggest that CGP provides relief to symptoms of IC which are exacerbated by certain types of foods. It appeared to reduce both pain and discomfort associated with IC and was accompanied by an increase in positive well being.

Conclusion

CGP appears to be safe and effective in reducing the symptoms of IC associated with food related exacerbations. Overall patients noted a significant reduction in urgency, frequency, pain, and an improvement in quality of life. A double blinded prospective randomized controlled study is in progress.

We recognize

Table 1. Demographic Characteristics of Survey Sample

Characteristic		N	%
Gender	Women	355	94.2
	Men	22	5.8
Age	20-35	31	8.2
	36-50	124	32.9
	51-65	109	28.9
	66-80	108	28.7
	80+	5	1.3
Race	Caucasian	357	97.3
	Non-Caucasian	10	2.7
Education level	Some High School	90	24.1
	Some College	162	43.3
	Advanced Degree	122	32.6
Household Income	<=$30,000	105	29.4
	>$30,000	252	70.6
Employment Status	Employed	154	41.2
	Homemaker	127	34.0
	Unemployed	92	24.6
	Retired	1	0.3

Table 2: Proportion of study participants reporting symptoms before and after use of calcium glycerophosphate (CGP)

Food	N	% before CGP	% after CGP	OR (95% CI)	P value
Pizza	71	67.6	15.5	15.5 (5.0-166.7)	<0.001
Coffee	81	84.0	37.0	*	<0.001
Carbonated beverages	48	77.1	47.9	15 (2.3-631.4)	<0.001
Alcohol	51	84.3	62.7	**	<=0.001
Acidic fruits and juices	46	89.1	37.0	25 (4.1-1026.7)	<0.001
Tomato-based products	124	74.2	37.9	5.5 (2.8-12.1)	<0.001
Chocolate	109	47.7	32.1	2.9 (1.3-7.0)	<=0.006
Spicy foods	68	82.4	17.6	13.5 (3.39-117.13)	<0.001

* : OR could not be computed due to missing data.

** : OR could not be computed because of a zero cell.

Table 3: Quality of Life Questionnaire

Characteristic	N	(+) Change	(-) Change	No Change	P-value
Full-time work	124	22	5	97	0.002
Social life	173	57	16	100	<0.0001
Travel	175	64	15	96	<0.0001
Sleep	174	71	10	93	<0.0001
Have sex	138	47	12	79	<0.0001
Exercise	171	69	13	89	<0.0001
Take care of family responsibilities	173	41	18	114	0.004
Positive mental attitude	180	63	21	96	<0.0001
Deal with stress	179	69	20	90	<0.0001