European Journal of Obstetrics & Gynecology and Reproductive Biology 207 (2016) 125–128

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Efficacy of an orally administered combination of hyaluronic acid, chondroitin sulfate, curcumin and quercetin for the prevention of recurrent urinary tract infections in postmenopausal women

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ARTICLE INFO

Article history:
Received 30 April 2016
Received in revised form 7 October 2016
Accepted 18 October 2016

Keywords:
Urinary tract infections
Glycosaminoglycans
Curcumin
Quercetin
Estrogen

ABSTRACT

Objective: To assess whether the orally administered combination of hyaluronic acid (HA), chondroitin sulfate (CS), curcumin and quercetin could be effective in preventing recurrent cystitis in postmenopausal women and whether its efficacy was conditioned by the concurrent use of local estrogen therapy.
Study design: This was a prospective evaluation of 145 postmenopausal women consecutively recruited from the database of three different investigators. All women should have mild-to-moderate urogenital atrophy and a history of recurrent urinary tract infections ($\geq$2 episodes within 6 months or $\geq$3 episodes within 12 months documented by positive urine cultures) during the last year. Patients were assigned to three different therapeutic regimens: the first group was treated only with vaginal estrogens, the second group only with HA, CS, curcumin and quercetin *per os*, and the third group was treated with HA, CS, curcumin and quercetin associated with local estrogens. We evaluated the number of patients with $<$2 infective episodes in the 6-month follow-up and $<$3 episodes in the 12-month follow-up (main aim definition) and the reduction of related symptoms through a Visual Analog Scale (VAS) and the Pelvic Pain and Urgency/Frequency (PUF) patient symptom scale. Student's *t*-test and chi-squared test were used for data analysis as appropriate.
Results: At 6-month follow up, the main aim rate was 8%, 11.1% and 25% in the three groups, respectively ($p < 0.05$ compared to baseline only in group 3). Although the reduction in the number of recurrent episodes became significant in all groups at 1 year follow-up, the main aim rate was almost double in women receiving both local estrogens and oral therapy (group 3) compared to those receiving single treatments. The improvement of related symptoms was significant in all groups at 12-month follow-up.
Conclusions: In postmenopausal women, the combination of HA, CS, curcumin and quercetin *per os* was effective in preventing recurrent urinary tract infections, especially if administered with vaginal estrogen therapy.

Introduction

Approximately 40% of women experience during lifetime at least one urinary tract infection episode requiring antibiotic treatment and the implicated pathogen is *Escherichia coli* in 75–90% of cases [1,2]. About one-third of these women develop recurrent infections, that is two or more episodes within 6 months or three or more episodes within 12 months documented by significant positive urine cultures ($\geq 10^3$ CFU/mL) [3]. The risk of developing a recurrent episode is greater when the first infection was caused by *E. coli* than another pathogen [4].

The period of a woman's life more targeted by the onset of recurrent cystitis certainly is post-menopausal age, when the fall of estrogen levels and its impact on urogenital mucosa predispose to bladder infections [5,6]. For these women suffering from recurrent urinary tract infections (UTIs) a significant deterioration of their social, sexual and working activities is unfortunately implicated.

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http://dx.doi.org/10.1016/j.ejogrb.2016.10.018
0301-2115/

In the management of these infections, the optimization of antibiotic strategies appears fundamental in view of the increasing bacterial resistance. As part of therapies to prevent recurrent episodes, the leading experts unanimously agree on the role of estrogens, especially when administered by vaginal rather than systemic route [7,8], but the recent introduction of substances able to strengthen bladder defense mechanisms, namely the glycosaminoglycans (GAGs), has opened new perspectives.

Based on the successful results of the intravesical administration of these GAGs, in particular hyaluronic acid (HA) and chondroitin sulfate (CS), for both interstitial and recurrent bacterial cystitis [9–16], we postulated that the same compound as an oral formulation, enhanced by the antioxidant properties of curcumin and quercetin, could be effective in preventing recurrent UTIs.

The aim of this study was to assess whether the oral therapy with HA, CS, curcumin and quercetin, eventually associated with local estrogen therapy, is effective in the prevention of recurrent UTIs in postmenopausal women.

Materials and methods

In this multi-center, prospective study we recruited postmenopausal women with symptoms and signs of hypoestrogenism and with a history of recurrent UTIs (according to the above-mentioned definition) in the previous twelve months. These infections had to be confirmed by positive urine cultures. The written patient consent to be enrolled in the study was obtained from all patients. The protocol for the research project has been approved by the Ethics Committee of the Second University of Studies of Naples, in accordance with the provisions of the Declaration of Helsinki.

All patients were previously submitted to a thorough clinical evaluation to be enrolled in the study. We selected women with mild-to-moderate urogenital atrophy, corresponding to a Vaginal Health Index (VHI) score between 10 and 15 [17], and a negative urine culture at baseline. Enrolled women were not taking antibiotics for their recurrent UTIs since at least one month. Exclusion criteria for the study were: pelvic organ prolapse $\geq$ II stage (according to the POP-Q system [18]), post-void residual >100 mL, stress or urge urinary incontinence, interstitial cystitis/painful bladder syndrome, past or current neoplastic disease, urinary tract stones, renal insufficiency, diabetes mellitus. Women who were in therapy with systemic estrogens were excluded too.

Three different investigators selected the patients consecutively from their databases administering them different therapies:

- group 1 (first investigator), local estrogen therapy only (0.005% estriol vaginal gel, daily for three weeks and then twice weekly up to 12 weeks; repeat treatment every three months);
- group 2 (second investigator), oral therapy with HA, CS, curcumin and quercetin only (2 capsules daily for 15 days a month for 3 months, then one capsule daily for 15 days a month for the next 9 months);
- group 3 (third investigator), local estrogen therapy (0.005% estriol vaginal gel) + oral therapy with HA, CS, curcumin and quercetin (same administration schedule as above).

The primary objective of the study was to evaluate the number of patients with less than two infective episodes in the 6-month follow-up and less than three episodes in the 12-month follow-up from the beginning of the therapy. We performed both per-protocol and intention-to-treat analysis.

The secondary endpoints were to evaluate the reduction of related symptoms and improvement in patients' quality of life at 12-months follow-up compared to baseline. The tools used for this purpose were:

- A Visual Analog Scale (VAS) to provide a subjective assessment of the severity of their symptoms, where the value 0 indicates the best health state and the value 100 the worst health state.
- The Pelvic Pain and Urgency/Frequency (PUF) patient symptom scale, a validated questionnaire used to evaluate patients with chronic pelvic pain (range 0–35, score >12 indicative of significant symptoms) [19].

We evaluated the trophism of vaginal mucosa through VHI score at baseline and 12-month follow-up. Urine culture was performed every month during the follow-up period, prescribing antibiotics to patients with positive results, but without removing them from the study. Follow-up visits were performed by clinicians who were not aware of prescribed treatment.

Continous data were reported as means ± standard deviation (SD) and analyzed with Student's *t*-test. Categoric relationships were analyzed by the chi-squared test. Probability values of <0.05 were considered statistically significant.

Results

A total of 145 subjects were recruited (group 1: 50 women; group 2: 48 women; group 3: 47 women). The demographic and clinical characteristics of the population are shown in Table 1 and no differences were seen among groups ($p > 0.05$).

As seen in Table 1, the vast majority of patients had their recurrent UTIs always caused by *E. coli*, with similar percentages among groups. Other pathogens colonizing the urinary tract, in particular *Enterococcus faecalis*, *Proteus mirabilis*, *Staphylococcus saprophyticus* and *Klebsiella pneumoniae*, were responsible for the remaining episodes in smaller percentages.

At 6-month follow-up, all patients in group 1 were still using local estrogens, while both in group 2 and in group 3 three patients dropped out of their therapies. The reduction in the number of patients with ≥2 urinary tract infection episodes (recurrent UTIs) was significant compared to baseline only in those receiving combination therapy (group 3) (Table 2).

One-hundred thirty out of the 145 women enrolled completed the 12-month follow-up, divided in 45, 44 and 41 into the three

Table 1
Baseline characteristics of the patients.

	Group 1 ($n=50$)	Group 2 ($n=48$)	Group 3 ($n=47$)
Ages (years, mean ± SD)	56.4 ± 3.2	56.6 ± 2.9	57.0 ± 4.1
Last-year UTI episodes (mean ± SD)	4.7 ± 1.4	4.6 ± 1.3	4.5 ± 1.4
Duration of recurrent UTIs (months, mean ± SD)	24.7 ± 5.6	26.4 ± 8.1	26.1 ± 6.4
Patients with UTIs due to *E. coli* [*n*/*N* (%)]	41/50 (82)	38/48 (79.2)	36/47 (76.6)
Sexually active patients [*n*/*N* (%)]	43/50 (86)	41/48 (85.4)	40/47 (85.1)
VAS score (mean ± SD)	80.2 ± 14.1	83.5 ± 11.9	82.4 ± 13
PUF score (mean ± SD)	20 ± 3.9	20.8 ± 3.9	21.7 ± 3.9
VHI score (mean ± SD)	11.8 ± 1.7	11.8 ± 1.4	11.6 ± 1.6

Table 2
Patients without recurrent UTIs at 6- and 12-month follow-up compared to baseline. Values are given as *n*/*N* (%). Per-protocol analysis (PP) and intention-to-treat analysis (ITT).

		6-month follow-up	*p*-value	12-month follow-up	*p*-value
Group 1	PP	4/50 (8)	0.15	13/45 (28.8)	0.001
	ITT	4/50 (8)	0.15	13/50 (26)	0.002
Group 2	PP	5/45 (11.1)	0.07	15/44 (34.1)[a]	0.0005
	ITT	5/48 (10.4)	0.08	15/48 (31.2)[b]	0.0008
Group 3	PP	11/44 (25)	0.003	27/41 (65.8)[c,d]	<0.0001
	ITT	11/47 (23.4)	0.005	27/47 (57.4)[e,f]	<0.0001

Group 1: local estrogen therapy.
Group 2: oral therapy with HA, CS, curcumin and quercetin.
Group 3: local estrogen therapy + oral therapy with HA, CS, curcumin and quercetin.
[a] $p = 0.598$ vs. group 1 – PP (RR 1.18; 95% CI 0.638–2.184).
[b] $p = 0.566$ vs. group 1 – ITT (RR 1.20; 95% CI 0.641–2.253).
[c] $p = 0.001$ vs. group 1 – PP (RR 2.28; 95% CI 1.371–3.791).
[d] $p = 0.006$ vs. group 2 – PP (RR 1.93; 95% CI 1.212–3.079).
[e] $p = 0.003$ vs. group 1 – ITT (RR 2.21; 95% CI 1.303–3.748).
[f] $p = 0.014$ vs. group 2 – ITT (RR 1.83; 95% CI 1.130–2.990).

groups, respectively. At 12 months, the difference in the number of patients who were cured according to the main aim definition (<3 infective episodes) became significant compared to baseline in all groups (Table 2).

Moreover, the number of patients who were "disease-free" at 12-month follow-up was significantly higher in group 3 compared to those receiving monotherapies, whereas there was no difference between group 1 and 2 (Table 2).

The improvement of related symptoms was significant in all groups at 12-month follow-up, as noticed by the reduction both in VAS scale value (Fig. 1) and in PUF score (Fig. 2). A significant increase in VHI scores was reported only in women receiving local estrogen therapy (Table 3).

Regarding the safety profiles of prescribed treatments, no patient in the three groups reported adverse events.

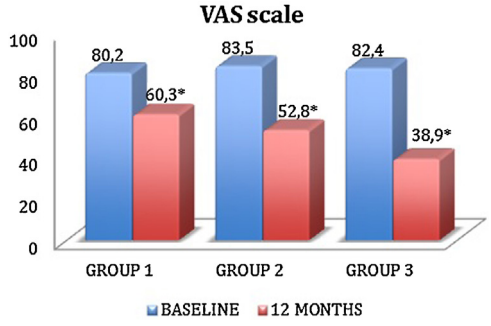

Fig. 1. VAS scale; *:$p < 0.05$ vs. baseline.

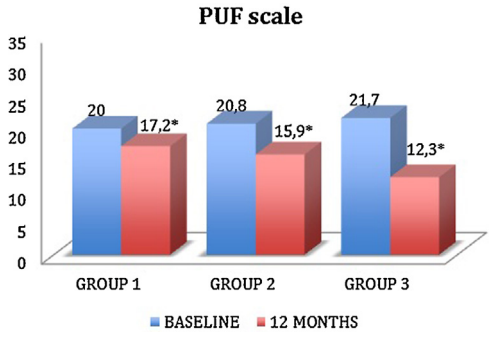

Fig. 2. PUF scale; *:$p < 0.05$ vs. baseline.

Table 3
VHI score. Values are given as mean ± SD. Per-protocol analysis.

	Baseline	12 months	*p*-value
Group 1 ($n = 45$)	11.8 ± 1.7	15.7 ± 3.0	<0.0001
Group 2 ($n = 44$)	11.8 ± 1.4	11.4 ± 1.0	0.40
Group 3 ($n = 41$)	11.6 ± 1.6	15.7 ± 2.8	<0.0001

Comment

The recurrence of UTIs has been associated to an impairment of GAG layer covering the urothelial mucosa with exposure of adhesion molecules and subsequent internalization of extracellular pathogen, particularly *E. coli*. As outlined in the introduction, several studies supported this hypothesis by showing the effectiveness of the intravesical administration of GAGs in preventing recurrent episodes [12–16].

Thanks to its three-layer structure, uroplakins and gap junctions on the apical membrane and the GAG layer on its surface, the urothelium represents a selectively permeable epithelium. It not only acts as a physical barrier but is able to generate various kinds of signals that are transmitted to the sensory nerves of the sub-urothelium and, after being processed, are responsible for contraction and relaxation of the detrusor muscle. Therefore any alteration in urothelial structure can generate symptoms such as pain, urinary frequency or urgency, that are typical of the above mentioned diseases [20].

The therapeutic rationale of GAGs derives from their role in contrasting the pathogenesis of recurrent cystitis through the restoration of the mucopolysaccharide film coating the healthy urothelium. Moreover, intravesical GAG therapy appears more effective than antibiotic prophylaxis in preventing recurrent episodes, as demonstrated in two previous studies, one by De Vita et al. and the other by our group, in which GAG therapy was compared with sulfamethoxazole + trimethoprim and fosfomycin, respectively [21,22]. The increased effectiveness of intravesical therapy is due to the fact that it acts by reinforcing the barrier function of the urothelium, unlike antibiotics that only determine the temporary eradication of the pathogen. However, they are unable to reach intracellular bacterial reservoirs that are often responsible for relapses [23]. Through the inhibition of bacterial colonization of the urothelium, GAG therapy appears to be able to prevent the onset of recurrent UTIs.

In the oral formulation, the action of GAGs is enhanced by the addition of quercetin and curcumin, natural substances of plant origin, that can prevent oxidative stress and inflammation.

Quercetin is absorbed in the small intestine and converted into various metabolites, of which the most active is quercetin-3-O-β-D-glucuronide [24,25]. It induces down-regulation of ICAM-1 expression and of other pro-inflammatory cytokines, it prevents mast cell degranulation blocking the release of histamine, and it inhibits lipid peroxidation [26–28].

Tetrahydrocurcumin (THC) derives from curcumin by hydrogenation [29]. Beyond its anti-inflammatory and antioxidant activities [30,31], it produces an analgesic effect via antagonizing the transient receptor potential vanilloid-1 (TRPV1) receptor [32].

On the basis of the above evidence, oral therapy with HA, CS, curcumin and quercetin appears to be a potentially effective treatment for patients with recurrent UTIs, also for maintenance after previous intravesical instillations of GAGs.

In our study we focused on postmenopausal women because they are more likely to develop recurrent cystitis due to the loss of estrogen's effects, as mentioned earlier. Symptoms of vaginal atrophy (dyspareunia, itching, vaginal burning and dryness) may coexist with lower urinary tract symptoms (irritative or not) up to 70% of cases [5]. The widely demonstrated efficacy of local estrogen

therapy in the management of postmenopausal women with genito-urinary symptoms should be sought in the common embryological origin of female genital and lower urinary tracts. This makes them both sensitive to the effects of estrogen [33].

The aim of our study was to demonstrate the efficacy of oral therapy with HA, CS, curcumin and quercetin in preventing recurrent cystitis in postmenopausal women and if it was conditioned by the concurrent use of local estrogen therapy.

At 6-month follow-up, we noticed a significant reduction in the number of patients still experiencing recurrent UTIs only in those receiving both treatments (group 3) and although it was recorded in all groups at 12 months, our results show that the combination therapy (vaginal estrogen + HA, CS, curcumin and quercetin *per os*) is more valid than single treatments, resulting in a cure rate of about 66%. The probability of being free from recurrent UTIs at 12-month follow-up was significantly greater for patients in group 3 compared to those receiving monotherapies. The drop-out rate from the study was low and similar among groups; this could explain why there was no difference between per-protocol and intention-to-treat analysis.

Local estrogen and oral GAG therapies work synergistically to prevent recurrent UTIs, by improving the trophism of urogenital mucosa and strengthening bladder defense mechanisms, respectively. As a direct result of vaginal estrogens, we observed a definite increase of VHI score in group 1 and 3 while it remained largely unchanged in women receiving only oral GAG therapy (group 2). Even the reduction of related symptoms was greater in the group receiving combination therapy, as it was significant in each group comparing with baseline. These results confirm the synergistic effect of the two treatments not only on the number of infective episodes but also on the related symptoms.

About the cost-effectiveness analysis of each treatment, our data show that monotherapies with local estrogen (group 1) and HA, CS, curcumin and quercetin *per os* (group 2) required an extension of treatment up to 12 months to significantly reduce the number of patients with recurrent UTIs. Conversely, combined therapy (group 3) was effective already at 6 months. It is well-known that low long-term treatment retention rates are mainly determined by unsatisfactory results in the short term. Although combined therapy is more expensive for the patient compared to monotherapy within a year, its earlier effectiveness could justify the use of this treatment rather than monotherapy, both reducing the overall medical care costs related to recurrent UTIs and increasing the long-term compliance and persistence to treatment.

In our experience, the orally administered combination of hyaluronic acid, chondroitin sulfate, curcumin and quercetin was effective in preventing recurrent urinary tract infections, both alone and in association with local estriol treatment. The simultaneous use of the two treatments can be particularly useful for women in whom urogenital atrophy is the *primum movens* of the susceptibility to bacterial contamination of the urinary tract.

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