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Original Article

Comparison of Anti-Inflammatory and Anti-Infection Impact of Cornu's Mas, Sucralfate, and Intravesical Hyaluronic Acid in Interstitial Cystitis Rat Model of Interstitial Cystitis

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HIGHLIGHTS

- Intravesical injection of HA and oral administration of sucralfate, and Cornu's mas were able to reduce the inflammation severity.
- To assess the effects of treatment with oral Cornu's mas and sucralfate, and intravesical hyaluronic acid (HA) on bladder histopathology and inflammatory cells.

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ABSTRACT

Introduction
To assess the effects of treatment with oral Cornu's mas and sucralfate, and intravesical hyaluronic acid (HA) on bladder histopathology and inflammatory cells in vivo model of Bladder pain syndrome/interstitial cystitis (BPS/IC).

Methods
A total of 25 female rats were grouped: control (group I), IC (group II), HA (group III), Sucralfate (group IV), and Cornu's mas (group V). Chemical cystitis was induced in four groups (all except the control group) by the intravesical instillation of Hydrogen peroxide, Cornu's mas extract for 7 days twice a day, sucralfate for seven days twice a day, and HA every week for a month and then every month for two months were administered. Bladder tissue was removed to check inflammatory cell infiltration by histopathological examination.

Results
A total of 25 female rats were grouped: control (group I), IC (group II), HA (group III), Sucralfate (group IV), and Cornu's mas (group V). Chemical cystitis was induced in four groups (all except the control group) by the intravesical instillation of Hydrogen peroxide, Cornu's mas extract for 7 days twice a day, sucralfate for seven days twice a day, and HA every week for a month and then every month for two months were administered. Bladder tissue was removed to check inflammatory cell infiltration by histopathological examination.

Conclusions
Intravesical injection of HA and oral administration of sucralfate, and Cornu's mas were able to reduce the inflammation severity but not the normal level in the rat model of BPS/IC.

Keywords: Cornu's Mas; Sucralfate; Hyaluronic Acid; Interstitial Cystitis; Experimental

Introduction

Bladder pain syndrome/interstitial cystitis (BPS/IC) is a urinary bladder disorder without any pathological cause characterized by several symptoms primarily including suprapubic pain, frequency, and urgency. The presence of chronic symptoms along with rolling out the other possible causes like cancer or infection, confirms the diagnosis of BPS/IC (1). Although enormous efforts have been made to clarify its etiology, the exact etiology is yet to be clear (2). The most accepted mechanism responsible for BPS/IC is a disruption in the defensive mucosal layer of the bladder, namely glycosaminoglycan (GAG). Ulceration, inflammation, and granulation are the most frequent pathology changes in this syndrome (3, 4). Despite tremendous advancements in the treatment of BPS/IC, up to now, no gold standard treatment for BPS/IC is introduced. Current guidelines suggest the combination of lifestyle interventions, pain management, and medications is the best way that the disease can be managed (5).

Intravesical injection of (HA), a component of the urothelial GAG layer, is postulated to be able to alleviate the symptoms and increase the quality of life in patients with BPS/IC (6) probably through decreasing inflammation and is recommended by the European Association of Urology (EAU) for BPS/IC treatment (5). Sucralfate, which is a complex of sulfated sucrose and aluminum hydroxide, is capable of protecting epithelial cells, especially gastrointestinal cells against detrimental agents (7). An experimental study has demonstrated the beneficial effect of sucralfate on chemical cystitis, which originates from its ability to prohibit leukocyte migration and aggregation and limit immune complexes' adherence to polymorphonuclear cells (8). Herbal and traditional medicine as a choice for the treatment of urinary tract infection (UTI), is gaining a great amount of attention. Recent studies have highlighted the capacity of Cornus mas in the treatment of UTI (9-13). Its anti-inflammatory effects may be useful for BPS/IC treatment; nonetheless, no study has investigated its impact on BPS/IC.

Interleukin (IL)-6 is a well-known pro-inflammatory cytokine that can be released by different cells mainly macrophages, fibroblast, and mast cells. It is representative of the severity of inflammation. It has been repeatedly shown that mast cells maintain a mandatory role in lots of inflammatory diseases (14). Similarly, activated mast cells and damage to the bladder's mucosa have been reported in patients suffering from BPS/IC (15-17).

We designed an animal study to evaluate the impact of three agents including HA, Sucralafte, and Cornu's mas on bladder histopathology and compare their efficacy with each other in a rat chemical cystitis model.

Methods

Animals

This study is based on ARRIVE guidelines. All animal experimentations and the study design were approved by the Ethical Committee of Tehran University of Medical Sciences (IR.TUMS.MEDICIEN.REC.1399.988). A total number of 25 adult female rats aged (4 weeks, weight 150-200g) of the Wistar strain were entered into the study. They were equally divided into five groups each containing five rats including control (group I), IC (group II), hyaluronic acid (group III), Sucralfate (group IV), and Cornu's mas (group V). Rats were housed 1 week before the procedures in groups of five per cage and given food and water ad libitum. Straw bedding in cages was changed once every two days. The animal lab was controlled at a constant temperature of 21app1°C and 50% humidity. The light-dark cycle was equally 12:12 hours. The rationale for the doses of Cornu's Mas, Sucralfate, and Intravesical Hyaluronic Acid (HA) was chosen based on previous publications (18). It was amounts of 20 mg kg−1 of body weight Cornu's mas extract (18), intravesically with hyaluronic acid (0.5ml, 0.8mg/ml) every week for a month and then every month for two months (19), and sucralfate 0.5ml gavage and 125mg dissolved in 100ml water to take orally, twice a day for seven days (20).

Induction of chemical cystitis

Chemical cystitis was induced in four groups (all except the control group) by the intravesical instillation of Hydrogen peroxide (1 ml of 1.5% H2O2), as a standard chemical cystitis model described by Homan et al., (21). Under anesthetization with isoflurane, after urination, H2O2 was instilled into the bladder lumen by a 24-G polypropylene catheter which was inserted transurethral, remaining for 30 minutes, then the bladder was washed with water and the process was repeated 30 minutes later. All procedures were done in sterile conditions. At the same time, to prevent urinary infection, the rats received intramuscular ciprofloxacin (20mg/kg) (21). After 48 hours, one rat from each group was randomly sacrificed for histopathological confirmation of chemical cystitis.

Treatment protocol

Three different treatment protocols were starting two days after induction of chemical cystitis. Group I (n=6): This group consisted of healthy animals, which were kept in the same situations without any chemical cystitis induction. Group II (n=6): Chemical cystitis was induced in the rats of this group and no treatment was administered to those. Group III (n=6): The rats of this group were treated with transurethral hyaluronic acid (0.5ml, 0.8mg/ml) every week for a month and then every month for two months (22). Group IV (n=6): This group was treated with sucralfate 0.5ml gavage and 125mg dissolved in 100ml water to be taken orally, twice a day for seven days. Group V (n=6): The animals of this group were treated with Cornu's mas extract 0.5ml gavage and 2ml solved

in 100ml water as an oral intake, twice a day for seven days (18).

After the end of treatments, all four remaining rats from each group were randomly selected and killed for histopathological examinations including gross examination, mast cell, and inflammatory changes) of bladder specimens. Euthanasia was performed with a CO2 bubble and bladder specimens were collected in formalin solution. No rats died during the experimental periods.

Histological examination

Urinary bladders were removed, fixed with 10% formalin, and embedded in paraffin. Tissues were cut into four-micron sections using a microtome and stained with hematoxylin and eosin (H&E) to evaluate inflammatory cells infiltration as well as Giemsa stain for identification of mast cells. The slides were examined by a uropathologist by light microscope (BX51, Olympus, Tokyo, Japan) and photographed by a smartphone. For assessing the leukocyte infiltration, we divided each specimen into 10 subspecimens and leukocyte infiltration was evaluated in each subspecimens separately at megafinance of × 400 using the following scale: 0: no leukocyte, 1: lower than 20 leukocytes, 2: 20-45 leukocytes, and 3: over 45 leukocytes. Then, the total score of 10 subspecimens was divided by 30 (the maximum possible score for 10 subspeimens) and multiplied by 100. We measured the mast cell counts by dividing each specimen into 10 subspecimens at ×200 magnification. We utilized the average number of mast cells for comparison between groups. We scored the specimens with no submucosal edema, mild submucosal edema, moderate submucosal edema, and severe submucosal edema as 0, 1, 2, and 3 respectively. The same pattern was considered for vascular congestion, mononuclear lymphoid cells, and granulation.

Statistical analysis

The discrete and continuous variables were reported using number (percent) and median (interquartile range (IQR)), respectively. The median (IQR) was used due to a low number of observations, as a barrier to achieving normality. The between-group comparisons were done using the nonparametric Mann–Whitney test for comparing the medians. The analyses were done using the statistical software Stata (ver.13). P-values less than 0.05 were considered to indicate statistical significance.

Results

While there was no case of erosion and ulcer in the control group, this symptom was observed for all participants of group II. Moreover, none of the three treatment groups recorded any case of erosion and ulcer. Considering edema, group I contained one mild case and three non-edema cases; group II had one moderate case and three severe cases; group III recorded one mild, two moderate cases, and one severe case; and finally, groups IV and V were comprised of three mild, and one moderate case (Figure 1, 2).

The median number (IQR) of mast cells in group II was significantly higher than in group I (41 (39.5-42) vs. 5 (4-7.5), respectively) (P-value=0.034). Likewise, the median number (IQR) of leukocytes in group II was significantly higher than in group I (29 (27.5-30) vs. 12.5 (10.5-17), respectively) (P-value=0.034). In addition, the median number (IQR) of mast cells and leukocytes in the treatment groups is presented in Table 1 and is compared with group I (Figure 3,4). As Table 1 shown, intravesical HA and oral administration of sucralfate, and Cornu's mas were able to regress leukocyte and mast cell counts to the levels of the control group (all P-values>0.4).

Discussion

BPS/IC, a common chronic bladder disease, was estimated to affect 11% and 5% of women and men, respectively, worldwide. BPS/IC treatment has always been challenging for urologists because of the uncertainty of its cause (23). Several theories have been proposed for BPS/IC and the most accepted theory seems to be disruption in the GAG layer of the bladder mucosa. An experimental study revealed that both inflammation and hyperactivity of the bladder will have occurred following destruction in the GAG layer (24). Parsons et al, demonstrated that permeability of the bladder in BPS/IC patients is impaired, as a result of the significant reduction in the GAG layer (25). In the current study, we evaluated the effects of two new therapy methods including Cornu's mas and sucralfate on BPS/IC. We provided novel evidence that the treatments including HA, Cornu's mas, and sucralfate were able to decrease the severity of inflammation but not the normal levels in the rat model of BPS/IC.

In the recent decade, several animal models of BPS/IC have been introduced. The emerging pieces of evidence support the fact that leukocyte and mast cell numbers of BPS/IC are similar to those of animal chemical cystitis models (26). As mentioned above, the animal model of BPS/IC can be created following transurethral instillation of hydrogen chloride, hydrogen peroxide, and acetic acid, intraperitoneal injection of cyclophosphamide, or lipopolysaccharide, and subcutaneous injection of uroplakin II (21, 26). Moreover, there is no absolute consensus concerning the best BPS/IC animal model and no animal model can reflect all of BPS/IC symptoms (27). In the current study, we used hydrogen peroxide to induce BPS/IC. Homan et al., showed that intravesical administration of H2O2 results in immediate pathological changes in contrast to bladder dysfunction, which lasts for a relatively long time. Bladder dysfunction lasts for about seven days and thus we were not able to perform

urodynamic tests (21, 28).

So far, several oral, injectable, and intravesical therapies with different efficacies have been proposed for the treatment of BPS/IC (5). Urologists are tended to treat BPS/IC with intravesical treatment that is found to be more effective in contrast to oral treatments. Moreover, the etiology of the disease is attributed to a disruption in the mucosa of the bladder. Although intravesical treatments have an association with lower rates of systematic side effects, it is an invasive procedure and carries a significant risk of infection (22). Among intravesical therapies, HA is one of the most promising treatments in that its beneficial effects on BPS/IC can last for at least three years. There is no consensus on the optimal regimen of intravesical HA (6). According to an experimental study that was conducted on 64 female rats, a significant reduction in inflammatory level, mast cell counts, values of IL-6 and intercellular adhesion molecule-1, pain sensitivity, and a significant increase in bladder capacity were observed when a single dose (0.8 mg/ml) of intravesical HA was administrated (29). In another study, a single dose of HA (0.5ml, 0.8mg/ml) was able to reduce inflammation and mast cell number significantly in rats with BPS/IC induced by hydrogen chloride (30). Yavuz et al., induced chemical cystitis with H2O2 and demonstrated that the combination therapy with HA and Chondroitin Sulphate improves inflammation of bladder urothelium in rats with IC (31); however, we did not find any significant reduction in inflammatory and mast cell counts after administration of HA. This inconsistency can be explained by different methods of IC induction, the different dosages of HA applied, and the different duration of the treatment.

The efficacy of sucralfate on gastric and duodenal ulcers is shown before (32). Sucralfate through several mechanisms, including increasing growth factors availability, stimulating prostaglandins production, inhibiting cell apoptosis, and decreasing oxygen free radicals, can facilitate wound healing and can be used as an agent for the management of epithelial ulcers (32). The majority of clinical and experimental studies are dedicated to assessing sucralfate's potential for gastroduodenal ulcer management. To our knowledge, only one study to date assesses its efficacy on chemical cystitis (20). Henningsohn et al., conducted a study to investigate the histological changes of the bladder following local sucralfate administration in rabbits with chemical cystitis. The authors applied sucralfate on days 1, 4, and 6 and found out subepithelial edema and inflammation, and mucosal bleeding, ulcerations, and necrosis were not detected in rabbits treated with sucralfate while these changes were found in 50% of the control group who were

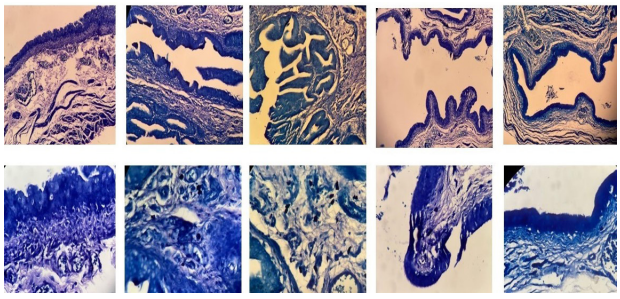

Figure 1. Representative images of Giemsa stained (above row: magnification ×100, below row: magnification ×400)

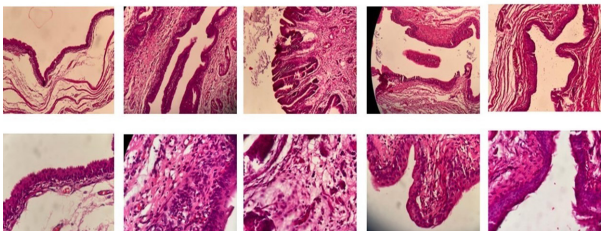

Figure 2. Representative images of hematoxylin-eosin stained (above row: magnification ×100, below row: magnification ×400).

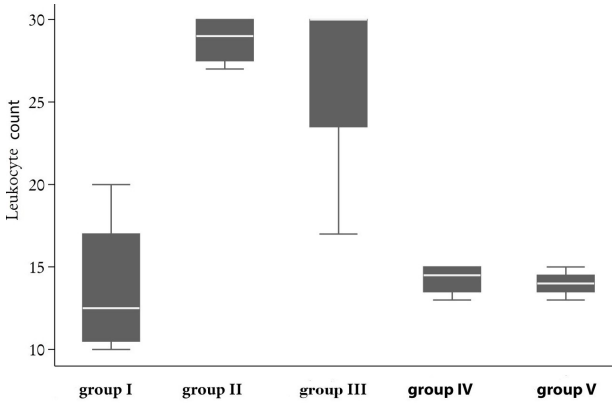

Figure 3. Boxplot of leukocyte counts by the group. Group I, control; group II, IC; group III, hyaluronic acid; group IV, Sucralfate; group V, Cornu's mas.

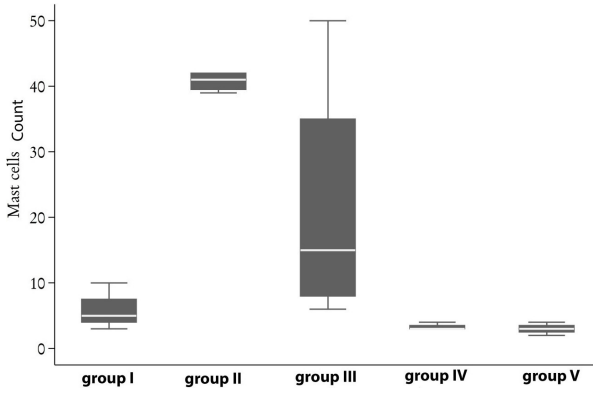

Figure 4. Boxplot of leukocyte counts by group. Group I, control; group II, IC; group III, hyaluronic acid; group IV, Sucralfate; group V, Cornu's mas.

Table1. Comparing the mast cells and leukocytes of the treatment groups with a group I (reported as median (IQR))

Groups	Mast cells	P-value	Leukocyte	P-value
I	5 (4-7.5)	Reference	12.5 (10.5-17)	Reference
II	41 (39.5-42)	0.034	29 (27.5-30)	0.033
III	15 (8-35)	0.480	30 (23-30)	0.473
IV	3 (3-3.5)	0.532	14.5 (13.5-15)	0.618
V	3 (2.5-3.5)	0.518	14 (13.5.-14.5)	0.686

*Comparisons between group I and II, I and III, I and IV, I and V were made.

not treated with sucralfate. Our findings were in line with the former study; however, the dosage of sucralfate, type of drug administration, and days of drug administration were different between the two studies.

Although the antioxidant feature of Cornu's mas was illustrated before (33), there are emerging clinical and experimental studies that investigate Cornu's mas therapeutic effects. For example, Dzydzan et al., demonstrated the anti-diabetic feature of Cornu's mas on rats (18). In another study, it has been suggested that Cornu's mas can be considered as an alternative therapy for antiplatelet therapy in cardiovascular disease (34). Few studies were determined to investigate the therapeutic effects of Cornu's mas in urological diseases (35, 36). Abdollahi et al., reported that Cornu's mas has protective effects on methotrexate-induced injury in rats (36). In a recent clinical report, Cornu's mas was utilized to treat women suffering from recurrent UTI. The authors found out that Cornu's mas administration is associated with lower dysuria and frequency, where, no significant decrease in recurrent UTI recurrence was appeared (36). In the present study, for the first time, the capacity of Cornu's mas as the agent for BPS/IC treatment was evaluated. We found Cornu's mas had not any significant effects on improving histopathological parameters of inflammation in the bladder.

The majority of experimental studies assessing the impacts of different treatments on BPS/IC have considered an enhanced number of mast cells and leukocytes as indicators of acute inflammation and decreased a number of these inflammatory cells as indicators of treatment response (37). It has been demonstrated that mast cells maintain a mandatory role in the pathophysiology of BPS/IC and it activation is associated with enhanced levels of several mediators and substance P. Evidence is in support of the fact that mast cell activation is associated with worsen BPS/IC symptoms (38). Yavuz et al., found out that intravesical injection of HA, Chondroitin Sulfate, and their combination in rats with BPS/IC reduced mast cell and leukocyte counts significantly (31). In contrast, in the present study, neither leukocyte count nor mast cell count was decreased significantly following treatment with HA, Cornu's mas, and sucralfate.

This study had some limitations that are worth mentioning. First, we did not evaluate the long-term histopathological impacts of these three agents on BPS/IC. Several studies assessed the long-term impact of intravesical HA on BPS/IC symptoms (6). Second, we administered three doses of intravesical HA and there is a possibility that different results would have emerged if we had applied extra doses of intravesical HA.

Conclusions

For the first time, we evaluated the potential of sucralfate and Cornu's mas for the management of BPS/IC in an animal model of chemical cystitis. We demonstrated that all treatments were potent to reduce the severity of inflammation as assessed by histopathological changes, mast cell count, and leukocyte count but not to the normal levels. We suggest further animal and clinical studies with the different dosages and duration of these agents are merits.

Authors' contributions

All authors contributed equally.

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Conflict of interest

All authors declare that there is no potential competing or conflict of interest.

Funding

There was no funding.

Ethics statement

All animal experimentations and the study design were approved by the Ethical Committee of Tehran University of Medical Sciences (IR.TUMS.MEDICIEN.REC.1399.988).

Data availability

Data will be provided on request.

Abbreviations

BPS/IC Bladder pain syndrome/interstitial cystitis
EAU European Association of Urology
GAG Glycosaminoglycan
H&E Hematoxylin and eosin
HA Hyaluronic acid
IQR Interquartile range
UTI Urinary tract infection

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