



Intravesical Instillation of Sodium Hyaluronate (Cystistat[®]) for the Treatment of Patients with Radiation Cystitis-Randomized Clinical Trial

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Abstract

Background: Radiotherapy (RT) is a choice to manage pelvic organ malignancies that can affect bladder; therefore, it causes radiation cystitis with some bothering urinary symptoms and decreasing the patient's quality of life. Intravesical hyaluronic acid (HA) is an agent with promising results in some studies for cystitis, and Cystistat is a derivative of hyaluronic acid.

Objectives: This clinical trial aimed at evaluating the effects of intravesical instillation of Cystistat on symptoms of radiation cystitis and quality of life (QOL).

Methods: A total of 58 patients with radiation cystitis were randomized in 2 groups (case: 30, control: 28). One group received intravesical Cystistat, the other received normal saline weekly for up to 4 weeks and then monthly for up to 2 months. Hematuria, Visual Analog scale (VAS) and QOL based on King's Health questionnaire were compared before and 3, 6 and 9 months after intravesical instillation.

Results: The mean age of the patients was 63.93 ± 10.89 years old. The mean of each sub-category of QOL and total score of QOL, as well as, VAS score were significantly improved in comparison to the control group at each time of follow-ups ($P < 0.05$). Hematuria was significantly different in the 3rd, 6th and 9th month of follow-ups ($P < 0.05$).

Conclusions: Findings showed that patients with radiation cystitis could significantly benefit from intravesical instillation of HA, their hematuria would be successfully resolved rather than control group in addition to lowering the VAS score, so their QOL would be improved.

Keywords: Sodium Hyaluronate, Hematuria, Hyaluronic Acid, Cystitis

1. Background

Malignancy and the management methods of cancer can lead to several side effects by direct and indirect mechanisms (1). Radiation cystitis is bladder lining urothelium inflammation as a complication of bladder irradiation due to pelvic organs malignancies (2). Pelvic organs malignancies are more common in men. However, prostate (3-7) and bladder cancer in men and uterine and ovarian cancer in women are more common than pelvic organs malignancies (8). Radiation therapy (RT) is a therapeutic option to manage the pelvic organs malignancies and bladder is one of the organs irritating during pelvic region radiation, 6% - 21% of these patients experienced lower urinary

tract symptoms (LUTS) and 9% of men who radiated due to prostate cancer suffered from moderate to severe radiation cystitis symptoms (2, 9, 10). Radiation-induced cystitis symptoms vary from microscopic hematuria and LUTS to gross hematuria, urinary incontinence, fistulae formation, and death (11).

The concept of a defective glycosaminoglycan (GAG) barrier is thought to be related to the pathogenesis of several vesical situations, including urinary tract infection, calculi, idiopathic detrusor overactivity, interstitial cystitis (IC), and chemical or radiation cystitis, as such may assign different approaches to the management of those diseases (12, 13).

There is an increasing body of evidence that introduces

different modalities to manage this situation and repair the GAG layer, including hyperbaric oxygen, intravesical heparin, hyaluronic acid (HA), oral pentosane polysulfate (Elmiron), and even surgery (13, 14).

A derivative of HA, sodium hyaluronate, has been produced to recharge the insufficient GAG layer and has been used successfully in the management of IC and newly in treating RT-induced Cystitis (15).

Among which, intravesical hyaluronic acid (HA) instillation revealed promising outcomes treatment for various uncomfortable symptoms in the bladder, such as interstitial cystitis. However, the evidence for radiation cystitis is limited and the definite regimen was not clarified (16, 17).

Radiation-induced cystitis symptoms have detrimental sequels on the quality of life (QOL) and a number of valid tools are introduced to evaluate these effects such as King's health questionnaire (KHQ) (18), but there are few studies reporting outcomes using valid QOL criteria following treatment with intravesical Cystistat.

The King's Health questionnaire is a health-related QOL instrument for the evaluation of cases with LUTS disease. The questionnaire has demonstrated validity and reliability in both genders and is available in 34 culturally and linguistically validated translations. All King's Health questionnaire domains are scored on a 0 (best) to 100 (worst) scales (19).

2. Objectives

Thus, this randomized controlled trial (RCT) aimed at assessing the potency of a specific regimen of Cystistat in controlling radiation cystitis symptoms by focusing on patients' QOL and its chronological change.

3. Methods

3.1. Population and Sample Size

In this RCT, from October 2017 to 2019, 72 patients, blind to treatment regimen, who underwent radiotherapy (conventional or intensity-modulated radiotherapy (IMRT)) due to pelvic malignancy after at least 6 months from RT were enrolled in this study. The RT was delivered in different centers and developed cystitis symptoms in grades II and III according to the radiation therapy oncology group (RTOG). Classification of durable complications and toxicity after RT was made in Shohada-e-Tajrish Hospital, Tertiary Referral Center, Tehran, Iran. Three subjects in the case and two in the control group were categorized in grade III cystitis symptoms.

Sample size calculations were based on the outcome of QOL score after 3-month intravesical instillation of Cystistat in a pilot study among 10 patients with grade II radiation cystitis. A 10% loss to follow-up was anticipated with a significance level of 0.05 and a power of 80%. Finally, the sample size to illustrate the superiority of a treatment arm to a control arm was 30 patients.

3.2. Exclusion Criteria

Patients with a history of benign prostate hyperplasia (BPH), urethral stricture disease, neurology and neurosurgery problems, diuretics drugs consumption, diabetes mellitus, and vesicoureteral reflux were excluded.

3.3. Study Protocol

Before any interventions, urine culture requested, cystoscopy and bladder wall random biopsy were carried out for all the patients. Finally, patients with negative urine culture and normal cystoscopy except radiation consequences and negative for malignancy pathology were reported and if patients did not respond to routine treatments of cystitis were included in the study. Before the treatment, all demographic data and type of cancer were collected. Grades of hematuria range from 0 to 100 and scores of pelvic pain, according to Visual Analogue scale (VAS), range from 0 to 10 were collected by questionnaire and all the patients fulfilled KHQ to evaluate QOL before treatment and 3, 6, and 9 months after treatment.

3.4. Randomization

The patients were randomly assigned to 2 arms using a random number table, and allocation was concealed by sealed envelopes. In the first group, 40 mg (50 ccs) of cystistat (Mylan, United States) with a vial of 2% lidocaine and one vial of heparin 5000 unit was injected into the bladder via 14 French nelaton catheters, and in the second group, cystistat was replaced with 50 ccs normal saline and the solution was kept in the bladder for one hour. According to the Ethics Committee comment, heparin was used as a standard treatment for both groups. In patients with gross hematuria, heparin was omitted from the solution. This solution was injected weekly for up to 4 weeks and then monthly for up to 2 months and after each instillation, the patients received antibiotics for 3 days to prevent infection. All cases visited at 3, 6, and 9 months after the intervention. Figure 1 shows the selection process of the patients in this study.

3.5. Primary and Secondary End-Point

Improvement in hematuria and VAS of pelvic pain as a primary goal and promotion of QOL score in the form of KHQ as a secondary goal were collected from all the subjects and was compared between the two arms.

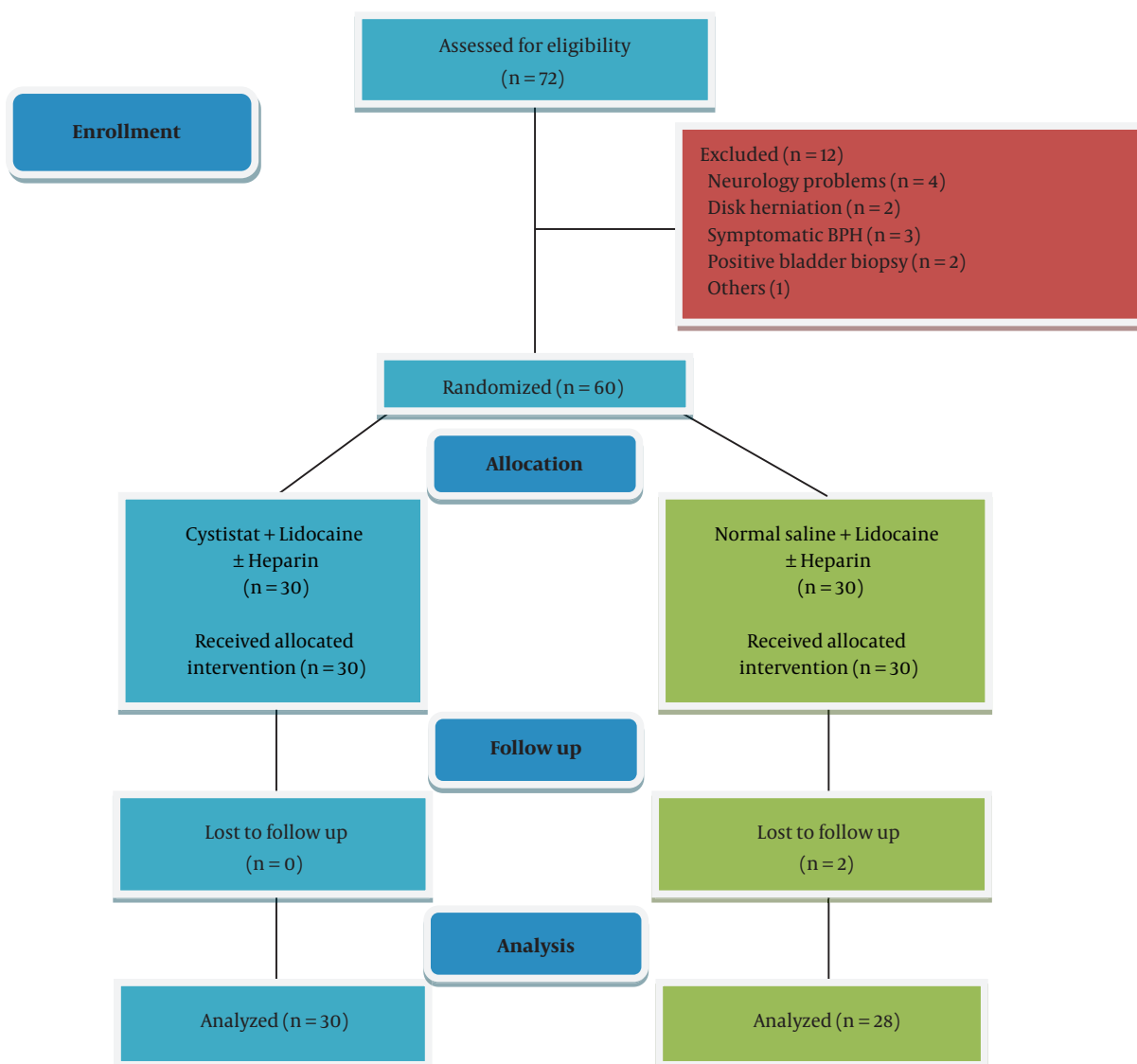


Figure 1. Flow chart of enrollment, allocation, follow up, and analysis of patients and the number of patients in the case and control groups

3.6. Statistical Analysis

We used SPSS21 software to analyze data, and quantitative variables were shown through mean \pm standard deviations (SD). Independent *t*-test, chi-square, and repeated measurement test were used to data analysis.

This study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences, Urology and Nephrology Research Center and also the written informed consent was taken from the patients.

4. Results

We enrolled 58 patients in this study (30 cases in the case group-28 cases in the control group). The mean age of them was 63.93 ± 10.89 years old (range: 38 - 82 years). Sixteen patients were female (53.3%) in the Cystistat group and 16 patients were male (57.1%) in the control group. Most common malignancies between men were prostate cancer (12 cases), rectal cancer (8 cases) and colon malignancy (6 cases) and in women were ovarian, uterine, and cervix (8, 6, and 6 patients, respectively).

The radiation therapy session and dosage were 25 - 28,

45 - 60 Gy in rectal cancer; 33 - 36, 55 - 70 Gy in prostate adenocarcinoma; 25 - 28, 50 - 60 Gy in cervix malignancy, 25 sessions, 45 Gy in endometrial cancer and 10 courses, 30 Gy in ovarian cancer.

There was no statistically significant difference between the sexes in the two study groups ($P = 0.29$). Table 1 shows the baseline data of the patients.

Table 1. Comparison of the Basic Characteristics of the Patients Between the Two Groups^a

Characteristics	Group	Values	P Value
Age	Case	62.73 ± 10.44	0.39
	Control	65.21 ± 11.40	
Total score of KHQ1	Case	452.00 ± 100.69	0.41
	Control	414.44 ± 90.70	
General health	Case	70.00 ± 23.11	0.80
	Control	66.96 ± 21.57	
Incontinence impact	Case	66.62 ± 23.17	0.58
	Control	69.00 ± 20.15	
Role limitations	Case	60.52 ± 20.75	0.77
	Control	58.89 ± 19.49	
Physical limitations	Case	62.36 ± 18.77	0.40
	Control	55.32 ± 15.06	
Social limitations	Case	66.97 ± 17.48	0.85
	Control	61.46 ± 17.55	
Relationships	Case	61.07 ± 17.13	0.56
	Control	58.90 ± 18.40	
Emotions	Case	66.97 ± 16.09	0.30
	Control	63.83 ± 16.99	
Sleep/energy	Case	63.85 ± 16.99	0.89
	Control	58.30 ± 16.65	
Severity measures	Case	71.07 ± 17.47	0.87
	Control	57.70 ± 17.26	
VAS2	Case	7.90 ± 1.626	0.41
	Control	7.54 ± 1.753	

Abbreviations: KHQ, King's Health questionnaire; VAS, Visual Analogue score.

^aValues are expressed as mean ± SD.

As the above table shows, there were no statistically significant differences between the groups at baseline ($P > 0.05$), and the distribution of data was normal.

Table 2 lists the changes in King's Health questionnaire Scores sub-categories at different times in 1, 3, and 6 months after intervention.

As Table 2 shows, the mean of each-sub-category of QOL, total score of QOL, and VAS were significantly improved in comparison to the control group at each time of

follow-up after 3, 6 and 9 months of intervention ($P < 0.05$).

The mean score of hematuria was 64.66 ± 20.80 in the case group and 67.85 ± 20.61 in the control group ($P = 0.56$). However, it was significantly different in the third, sixth, and ninth month follow-ups (in the third month: 56 ± 13.28 vs. 65.71 ± 15.25 ; in the sixth month: 42 ± 12.14 vs. 67.14 , in the ninth month: 40 ± 11.74 vs. 65 ± 11.70 in case and control groups, respectively).

Repeated measure test showed that total QOL score was significantly better in the cystistat group than in the control group ($P < 0.001$) by the time of follow-ups (Figure 2A).

The findings demonstrated that at follow-ups times VAS score was significantly decreased in the cystistat group compared to the control group ($P < 0.001$) (Figure 2B).

The findings also indicated that hematuria score was significantly decreased in the cystistat group ($P < 0.001$) by the time of follow-ups (Figure 2C).

4.1. Adverse Events

Two participants in the control group and one patient in the case group were involved urinary tract infection during intravesical instillation of agents that were managed with proper antibiotics based on antibiograms from urine culture. One woman from the case group developed bladder stone formation after three months without any previous history and a risk factor that litholopaxy was carried out for her and after that, the patient did not have any complaint.

5. Discussion

The pathogenesis of radiation cystitis damages the GAG layer of the bladder mucosa. This layer protects the bladder wall from toxic agents and microorganisms; therefore, it seems that any defects in this layer cause cystitis symptoms (20). Radiation cystitis is one of the main challenges in urology due to its unknown cause. Different remedial efforts such as radiation dose limitation and adjustment of irradiation field, oral drugs such as orgotein, vitamin E, and steroids trialed, however, were not completely successful in the treatment. The only approved oral therapy for radiation cystitis is Elmiron or pentose polysulfate sodium (17). Intravesical use of bacillus Calmette-Guerin was also utilized for this indication; however, the findings were controversial (21). The other intravesical therapeutic approach tested is constructed on the instillation of dimethyl sulfoxide (DMSO), which is conclusive in the management of many symptoms, but the reality that it is an organic solvent raises worries for its long-time use (21).

Among different therapeutic options, intravesical use of some agents was reported and their response rates were

Table 2. Compared Data From 3, 6, and 9 Months of Follow-Up Between the Two Groups^a

Characteristics	Group	After 3 Months	P Value	After 6 Months	P Value	After 9 Months	P Value
Total score of KHQ1	Case	455.23 ± 54.47	0.659	252.78 ± 52.36	< 0.0001	243.17 ± 60.77	< 0.0001
	Control	410.50 ± 76.38		409.67 ± 62.84		419.69 ± 60.21	
General health	Case	36.67 ± 14.28	< 0.0001	20.00 ± 13.77	0.019	20.00 ± 15.25	< 0.0001
	Control	55.36 ± 19.67		61.61 ± 18.61		61.61 ± 19.816	
Incontinence impact	Case	33.30 ± 17.49	< 0.0001	19.98 ± 16.59	< 0.0001	25.53 ± 20.84	0.025
	Control	61.85 ± 19.69		64.23 ± 17.98		67.80 ± 16.94	
Role limitations	Case	50.52 ± 14.82	0.118	35.53 ± 13.67	< 0.0001	34.41 ± 13.81	< 0.0001
	Control	56.51 ± 13.84		59.47 ± 12.34		60.66 ± 11.28	
Physical limitations	Case	46.08 ± 17.87	0.051	32.20 ± 17.48	< 0.0001	27.74 ± 14.74	< 0.0001
	Control	54.73 ± 14.93		55.93 ± 13.75		59.48 ± 13.15	
Social limitations	Case	47.18 ± 17.48	0.005	34.60 ± 13.34	< 0.0001	35.33 ± 14.26	< 0.0001
	Control	60.07 ± 16.27		59.08 ± 14.10		61.07 ± 14.87	
Relationships	Case	48.86 ± 15.11	0.001	33.30 ± 14.52	< 0.0001	32.74 ± 14.84	< 0.0001
	Control	62.46 ± 14.06		57.70 ± 13.95		57.70 ± 14.67	
Emotions	Case	54.58 ± 11.00	0.040	43.11 ± 8.47	0.002	42.19 ± 9.853	0.021
	Control	61.86 ± 15.16		60.87 ± 12.30		63.83 ± 14.37	
Sleep/energy	Case	51.63 ± 14.06	0.077	33.30 ± 15.79	< 0.0001	31.63 ± 17.70	< 0.0001
	Control	58.90 ± 16.64		59.48 ± 17.22		58.90 ± 16.64	
Severity measures	Case	56.35 ± 14.95	0.917	38.57 ± 15.08	< 0.0001	39.03 ± 16.20	< 0.0001
	Control	55.92 ± 16.33		55.32 ± 15.24		58.00 ± 18.21	
VAS2	Case	4.60 ± 1.35	< 0.0001	3.00 ± 1.74	< 0.0001	3.07 ± 1.17	< 0.0001
	Control	7.32 ± 1.41		7.50 ± 1.23		7.39 ± 1.16	

Abbreviations: KHQ, King's Health questionnaire; SD, standard deviation; VAS, Visual Analogue score.

^aValues are expressed as mean ± SD.

45% for chondroitin sulfate, 56% for heparin, and 44% for pentosane polysulfate (22).

In this trial, we presented that the use of cystistat; HA; in contrast to the control arm, significantly improved the QOL and VAS and hematuria score after 9 months. HA is a main mucopolysaccharide in the epithelial, connective, and neural tissues and stands for one of the major portions of the extracellular matrix that significantly be conducive to cell proliferation and migration. Moreover, it plays the part of a defensive barrier versus irritating factors that can destroy the epithelium. It might leucocyte migration, suppress immune complexes, and boost modulation of the fibroblasts, proliferation of the endothelial cell, and improvement of the curing tissues. Impairment of the GAG layer may result in direct exposure to components of urine, to bacteria and fungi (17). This injury can lead to radiation cystitis. Therefore, HA can be an option for the treatment of radiation cystitis. Kallestrup et al. (16) reported higher response rates with instillation HA treatment, and the valu-

able effect was conserved for ≥ 3 years. Morales et al. (23) showed that 71% of the participants who underwent HA instillations, demonstrated improvement of symptoms and disclosing the direct correlation between GAG layers, HA, and control of the IC.

Sommariva et al. (24) prospective trial showed that sodium hyaluronate declines the symptoms of RT-cystitis. Generally, 67 (97%) patients presented complete relief of pain and dysuria.

Engelhardt et al. (25) mentioned that after HA treatment, 50% of the subjects revealed bladder symptom remission without any additional treatment in 5-year follow-up and 41.7% of subjects with symptom recurrence revealed recovery with HA maintenance treatment. Miodosky et al. (26) in their study concluded that HA instillations can show instant benefit in releasing the pain, macroscopic hematuria, and voiding frequency, and acceptable advantageous duration of the treatment. Vassillis et al. (17) showed that the mean score of radiation cystitis before

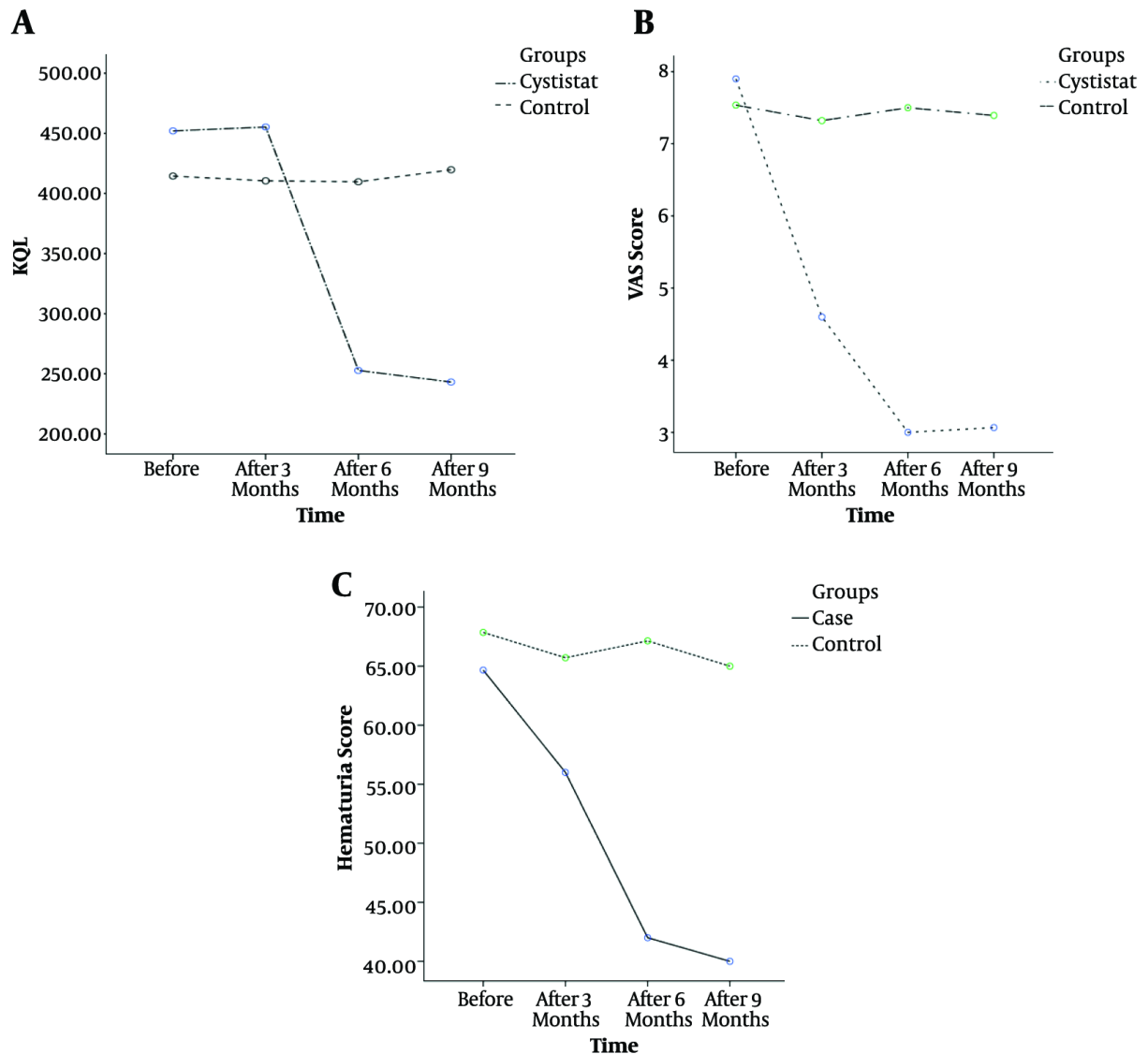


Figure 2. A, The alterations of the total score of the quality of life; B, VAS; and C, Hematuria in patients of cystistat and the control group by the time of follow-ups

and after the cystistat instillations was 2.70 ± 0.47 and 1.45 ± 0.51 , respectively ($P < 0.01$)¹⁷. Pyo and Cho in a meta-analysis showed a significantly positive effect in 6-month follow-up in interstitial cystitis patient (27).

Shao et al. have also demonstrated that intravesical administration of sodium hyaluronate is as influential as hyperbaric oxygen therapy in the management of RT cystitis. In this randomized study of 36 cases with pelvic malignancies, this management plan was well tolerated and resulted in a reducing of pelvic pain, bladder bleeding, and urinary frequency for ≥ 12 months (28).

Kallestrup et al. (16) demonstrated that HA reduced the

pain associated with IC, nocturia, and frequency for at least a span of 3 years.

5.1. Conclusions

This was the first study in the Iranian population indicating that patients with radiation cystitis could significantly benefit from HA, and their hematuria would be successfully resolved rather than control group, in addition to lowering the VAS score, so their QOL would be improved. Although the follow-up time was short-midterm for 9 months, the results showed the effect of time in an improving pattern. In view of the HA instillations efficacy

and the absence of systemic harm effects, the management of cystitis in radiation cystitis is suggested.

5.2. Limitation and Recommendation

As a limitation, the potential effect of heparin itself on the outcome of the study in both groups can interfere with the study results.

Another study limitations are few numbers of patients in each group and short follow-up of patients, but in addition to these limitations, this study was a RCT and compared all the sub-categories of KHQ of life questionnaire between the two groups; therefore, based on the data, we can candidate patients with radiation cystitis for cystitis instillation according to their most annoying problems decreasing their QOL.

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Footnotes

Authors' Contribution: Study concept and design: Farzad Allameh and Abbas Basiri. Acquisition of data: Seyyed Ali Hojjati. Analysis and interpretation of data: Atefeh Javadi. Drafting of the manuscript: Saleh Ghiasy. Critical revision of the manuscript for important intellectual content: Seyyed Ali Hojjati. Statistical analysis: Amir Hossein Rahavian. Administrative, technical, and material support: Saleh Ghiasy. Study supervision: Farzad Allameh.

Clinical Trial Registration Code: The clinical trial registration Code was IRCT20180218038788N1.

Conflict of Interests: There were no conflicts of interest.

Ethical Approval: This study involved human participants and was approved by the Ethics Committee of Shahid Beheshti University of Medical Science. (ethical code: R.SBMU.UNRC.1395.78).

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Informed Consent: All the patients signed a consent form before intervention.

References

- Allameh F, Azghandi S, Fallah Karkan M. Is chemotherapy related with erectile dysfunction in non-urolologic cancer patients? *Int J Cancer Manage.* 2018;**11**(9).
- Crew JP, Jephcott CR, Reynard JM. Radiation-induced haemorrhagic cystitis. *Eur Urol.* 2001;**40**(2):111-23. doi: [10.1159/000049760](https://doi.org/10.1159/000049760). [PubMed: [11528186](https://pubmed.ncbi.nlm.nih.gov/11528186/)].
- Allameh F, Rahavian AH, Ghiasy S. Prevalence of Castration Success Rate in Iranian Metastatic Prostate Cancer Patients -A Referral Center Statistics. *Int J Cancer Manage.* 2018;**In Press**(In Press). doi: [10.5812/ijcm.83613](https://doi.org/10.5812/ijcm.83613).
- Javanmard B, Razzaghi MR, Javanbakht O, Fallah Karkan M, Ghiasy S. Pathological Association Between Radical Prostatectomy and Needle Biopsy Specimen in Prostate Cancer Patients. *Int J Cancer Manage.* 2020;**13**(1). doi: [10.5812/ijcm.91609](https://doi.org/10.5812/ijcm.91609).
- Pourmand G, Salem S, Mehrsai A, Lotfi M, Amirzargar MA, Mazdak H, et al. The risk factors of prostate cancer: a multicentric case-control study in Iran. *Asian Pac J Cancer Prev.* 2007;**8**(3):422-8. [PubMed: [18159981](https://pubmed.ncbi.nlm.nih.gov/18159981/)].
- Jamali L, Moradi A, Ganji M, Ayati M, Kazeminezhad B, Fazeli Attar Z, et al. Potential Prognostic Role for SPOP, DAXX, RARRES1, and LAMP2 as an Autophagy Related Genes in Prostate Cancer. *Urol J.* 2020;**17**(2):156-63. doi: [10.22037/uj.v0i0.4935](https://doi.org/10.22037/uj.v0i0.4935). [PubMed: [30882175](https://pubmed.ncbi.nlm.nih.gov/30882175/)].
- Salehi B, Fokou PVT, Yamthe LRT, Tali BT, Adetunji CO, Rahavian A, et al. Phytochemicals in Prostate Cancer: From Bioactive Molecules to Upcoming Therapeutic Agents. *Nutrients.* 2019;**11**(7). doi: [10.3390/nu11071483](https://doi.org/10.3390/nu11071483). [PubMed: [31261861](https://pubmed.ncbi.nlm.nih.gov/31261861/)]. [PubMed Central: [PMC6683070](https://pubmed.ncbi.nlm.nih.gov/PMC6683070/)].
- DeSantis CE, Lin CC, Mariotto AB, Siegel RL, Stein KD, Kramer JL, et al. Cancer treatment and survivorship statistics, 2014. *CA Cancer J Clin.* 2014;**64**(4):252-71. doi: [10.3322/caac.21235](https://doi.org/10.3322/caac.21235). [PubMed: [24890451](https://pubmed.ncbi.nlm.nih.gov/24890451/)].
- Ghiasy S, Abedi AR, Moradi A, Hosseini SY, Karkan MF, Sadri G, et al. Is active surveillance an appropriate approach to manage prostate cancer patients with Gleason Score 3+3 who met the criteria for active surveillance? *Turk J Urol.* 2019;**45**(4):261-4. doi: [10.5152/tud.2018.72920](https://doi.org/10.5152/tud.2018.72920). [PubMed: [30461380](https://pubmed.ncbi.nlm.nih.gov/30461380/)]. [PubMed Central: [PMC6619850](https://pubmed.ncbi.nlm.nih.gov/PMC6619850/)].
- Fallah Karkan M, Razzaghi MR, Javanmard B, Tayyebiazar A, Ghiasy S, Montazeri S. Holmium: YAG laser incision of bladder neck contracture following radical retropubic prostatectomy. *Nephro Urol Mon.* 2019;**11**(1).
- Weiss JP, Boland FP, Mori H, Gallagher M, Brereton H, Preate DL, et al. Treatment of Radiation-Induced Cystitis with Hyperbaric Oxygen. *J Urol.* 1985;**134**(2):352-4. doi: [10.1016/s0022-5347\(17\)47166-7](https://doi.org/10.1016/s0022-5347(17)47166-7).
- Bassi PF, Costantini E, Foley S, Palea S. Glycosaminoglycan Therapy for Bladder Diseases: Emerging New Treatments. *Eur Urol Suppl.* 2011;**10**(6):451-9. doi: [10.1016/j.eursup.2011.06.001](https://doi.org/10.1016/j.eursup.2011.06.001).
- Salehi B, Butnariu M, Corneanu M, Sarac I, Vlaisavljevic S, Kitic D, et al. Chronic pelvic pain syndrome: Highlighting medicinal plants toward biomolecules discovery for upcoming drugs formulation. *Phytother Res.* 2020;**34**(4):769-87. doi: [10.1002/ptr.6576](https://doi.org/10.1002/ptr.6576). [PubMed: [31799719](https://pubmed.ncbi.nlm.nih.gov/31799719/)].
- Moldwin RM, Sant GR. Interstitial cystitis: a pathophysiology and treatment update. *Clin Obstet Gynecol.* 2002;**45**(1):259-72. doi: [10.1097/00003081-200203000-00027](https://doi.org/10.1097/00003081-200203000-00027). [PubMed: [11862078](https://pubmed.ncbi.nlm.nih.gov/11862078/)].
- Payne H, Adamson A, Bahl A, Borwell J, Dodds D, Heath C, et al. Chemical- and radiation-induced haemorrhagic cystitis: current treatments and challenges. *BJU Int.* 2013;**112**(7):885-97. doi: [10.1111/bju.12291](https://doi.org/10.1111/bju.12291). [PubMed: [24000900](https://pubmed.ncbi.nlm.nih.gov/24000900/)]. [PubMed Central: [PMC4155867](https://pubmed.ncbi.nlm.nih.gov/PMC4155867/)].
- Kallestrup EB, Jorgensen SS, Nordling J, Hald T. Treatment of interstitial cystitis with Cystistat: a hyaluronic acid product. *Scand J Urol Nephrol.* 2005;**39**(2):143-7. doi: [10.1080/00365590410015876-1](https://doi.org/10.1080/00365590410015876-1). [PubMed: [16032779](https://pubmed.ncbi.nlm.nih.gov/16032779/)].
- Vassilis K, Eftychia M, Andreas F, Ivelina B, Charalampos A. Use of Hyaluronic Acid (Cystistat) for the Treatment of Late Radiation Induced Cystitis in Patients after Prostate Irradiation. *J Bioequivalence Bioavailabil.* 2014;**6**(1). doi: [10.4172/jbb.1000174](https://doi.org/10.4172/jbb.1000174).
- Pourmomeny AA, Zargham M, Fani M. Reliability and Validity of the Quality of Life Questionnaire in Iranian Patients with Lower Urinary Tract Symptoms. *Low Urin Tract Symptoms.* 2018;**10**(1):93-100. doi: [10.1111/luts.12147](https://doi.org/10.1111/luts.12147). [PubMed: [28386953](https://pubmed.ncbi.nlm.nih.gov/28386953/)].

19. Homma Y, Uemura S. Use of the short form of King's Health Questionnaire to measure quality of life in patients with an overactive bladder. *BJU Int.* 2004;**93**(7):1009-13. doi: [10.1111/j.1464-410X.2003.04771.x](https://doi.org/10.1111/j.1464-410X.2003.04771.x). [PubMed: [15142153](https://pubmed.ncbi.nlm.nih.gov/15142153/)].
20. Parsons CL. Interstitial cystitis: epidemiology and clinical presentation. *Clin Obstet Gynecol.* 2002;**45**(1):242-9. doi: [10.1097/00003081-200203000-00025](https://doi.org/10.1097/00003081-200203000-00025). [PubMed: [11862076](https://pubmed.ncbi.nlm.nih.gov/11862076/)].
21. Peeker R, Haghsheno MA, Holmang S, Fall M. Intravesical bacillus Calmette-Guerin and dimethyl sulfoxide for treatment of classic and nonulcer interstitial cystitis: a prospective, randomized double-blind study. *J Urol.* 2000;**164**(6):1912-5. discussion 1915-6. doi: [10.1016/s0022-5347\(05\)66916-9](https://doi.org/10.1016/s0022-5347(05)66916-9). [PubMed: [11061879](https://pubmed.ncbi.nlm.nih.gov/11061879/)].
22. Parsons CL, Housley T, Schmidt JD, Lebow D. Treatment of interstitial cystitis with intravesical heparin. *Br J Urol.* 1994;**73**(5):504-7. doi: [10.1111/j.1464-410x.1994.tb07634.x](https://doi.org/10.1111/j.1464-410x.1994.tb07634.x). [PubMed: [8012771](https://pubmed.ncbi.nlm.nih.gov/8012771/)].
23. Morales A, Emerson L, Nickel JC. Intravesical hyaluronic acid in the treatment of refractory interstitial cystitis. *Urology.* 1997;**49**(5A Suppl):111-3. doi: [10.1016/s0090-4295\(97\)00183-0](https://doi.org/10.1016/s0090-4295(97)00183-0). [PubMed: [9146012](https://pubmed.ncbi.nlm.nih.gov/9146012/)].
24. Sommariva ML, Sandri SD, Ceriani V. Efficacy of sodium hyaluronate in the management of chemical and radiation cystitis. *Minerva Urol Nefrol.* 2010;**62**(2):145-50. [PubMed: [20562794](https://pubmed.ncbi.nlm.nih.gov/20562794/)].
25. Engelhardt PF, Morakis N, Daha LK, Esterbauer B, Riedl CR. Long-term results of intravesical hyaluronan therapy in bladder pain syndrome/interstitial cystitis. *Int Urogynecol J.* 2011;**22**(4):401-5. doi: [10.1007/s00192-010-1294-y](https://doi.org/10.1007/s00192-010-1294-y). [PubMed: [20938644](https://pubmed.ncbi.nlm.nih.gov/20938644/)].
26. Miodosky M, Abdul-Hai A, Tsirigotis P, Or R, Bitan M, Resnick IB, et al. Treatment of post-hematopoietic stem cell transplantation hemorrhagic cystitis with intravesicular sodium hyaluronate. *Bone Marrow Transplant.* 2006;**38**(7):507-11. doi: [10.1038/sj.bmt.1705474](https://doi.org/10.1038/sj.bmt.1705474). [PubMed: [16921402](https://pubmed.ncbi.nlm.nih.gov/16921402/)].
27. Pyo JS, Cho WJ. Systematic Review and Meta-Analysis of Intravesical Hyaluronic Acid and Hyaluronic Acid/Chondroitin Sulfate Instillation for Interstitial Cystitis/Painful Bladder Syndrome. *Cell Physiol Biochem.* 2016;**39**(4):1618-25. doi: [10.1159/000447863](https://doi.org/10.1159/000447863). [PubMed: [27627755](https://pubmed.ncbi.nlm.nih.gov/27627755/)].
28. Shao Y, Lu GL, Shen ZJ. Comparison of intravesical hyaluronic acid instillation and hyperbaric oxygen in the treatment of radiation-induced hemorrhagic cystitis. *BJU Int.* 2012;**109**(5):691-4. doi: [10.1111/j.1464-410X.2011.10550.x](https://doi.org/10.1111/j.1464-410X.2011.10550.x). [PubMed: [21895939](https://pubmed.ncbi.nlm.nih.gov/21895939/)].