

Preventive effect of Malva on urinary toxicity after radiation therapy in prostate cancer patients: A multi-centric, double-blind, randomized clinical trial

Bahram Mofid¹, Hossein Rezaeizadeh², Amir Mohammad Jaladat³, Fatemeh Atarzadeh⁴, Reihane Moeini⁵, Abbas Motevalian⁶, Ahmad Mosalaie⁷, Farshid Farhan⁸, Afshin Rakhsha⁹, Amir Shahram Yousefi Kashi¹⁰

¹ Associate Professor, Shohada-e-Tajrish Hospital, Department of Radiation Oncology, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

² M.D, Ph.D. of Traditional Persian Medicine, Assistant Professor, Department of Traditional Persian Medicine, School of traditional Medicine, Tehran University of Medical Science, Tehran, Iran

³ M.D, Ph.D. of Traditional Persian Medicine, Assistant Professor, Department of Traditional Persian Medicine, School of Medicine, Shiraz, Iran

⁴ M.D, Department of Traditional Persian Medicine, School of traditional Medicine, Tehran University of Medical Science, Tehran, Iran

⁵ M.D, Ph.D. of Traditional Persian Medicine, Department of Traditional Persian Medicine, School of traditional Medicine, Tehran University of Medical Science, Tehran, Iran

⁶ Associate Professor, Department of Public Health, Faculty of Public Health, Iran University of Medical Sciences, Tehran, Iran

⁷ Professor, Namazi Hospital, Department of Radiation Oncology, Faculty of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

⁸ Assistant professor, Cancer Institute, Imam Khomeini Hospital, Department of Radiation Oncology, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran

⁹ Assistant Professor, Shohada-e-Tajrish Hospital, Department of Radiation Oncology, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

¹⁰ Assistant Professor, Shohada-e-Tajrish Hospital, Department of Radiation Oncology, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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Abstract

Background: For patients receiving external beam radiation therapy (EBRT) after radical prostatectomy as adjuvant treatment or patients receiving EBRT as definitive treatment, partial irradiation of the urinary bladder is common. Many of such patients experience some degree of radiation-induced cystitis during or after EBRT. There is currently no efficient treatment for preventing radiation cystitis.

Objective: The aim of this study was to evaluate the effectiveness of one of the safe mucilaginous herbs (Malva) in preventing radiation-induced dysuria in patients who are undergoing EBRT for prostate cancer.

Methods: From April 2013 to August 2014, 68 patients were randomized into two groups using four block randomization, 34 to the drug (Malva) group and 34 to the placebo group. Of the 68 patients who began the study, 60 completed it. They were instructed to use the medication, i.e., Malva or the placebo, three times a day for six weeks. They were followed by a physician every two weeks for eight weeks, and urinary function was assessed in each visit by asking questions based on the Visual Prostate Symptom Score (VPSS) and a dysuria severity score. The changes in the VPSS and dysuria severity score between baseline and each follow-up visit were compared between the two groups in the study using repeated measures analysis of variance (ANOVA) and t-tests.

Corresponding author:

Assistant Professor Dr. Amir Shahram Yousefi Kashi, Shohada-e-Tajrish Hospital, Department of Radiation Oncology, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Tel: +98.2122739200, Fax: +98.2122739200, Email: shahpoo2002@yahoo.com

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Results: The median age of the 68 patients was 66. Twenty-one of 27 patients in the control group (77.7%) suffered from dysuria, while dysuria was detected in 23 of 33 patients (69.6%) who received Malva (odds ratio=2.70 for dysuria). After two weeks, four weeks, and six weeks of treatment with Malva, dysuria due to EBRT was milder in the treatment group than in the control group, and the differences were statistically significant ($p = 0.005$, $p = 0.004$, $p = 0.001$, respectively).

Conclusion: To the best of our knowledge, our study is the first study to assess the protective effect of a mucilaginous herb (Malva) against urinary toxicity induced by EBRT. The positive results of this study warrant further studies in this field.

Clinical Trial Registration: The study was registered in the Iranian Clinical Trial Registry Center (IRCT2012100711026N1).

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Keywords: Malva, dysuria, radiation therapy, prostate cancer

1. Introduction

Prostate cancer is now the most commonly diagnosed visceral cancer in western men, and the incidence is increasing even in low-risk populations. Radical prostatectomy and external beam radiation therapy (EBRT) with or without brachytherapy are the treatment modality of choice for many cases of clinically localized prostate cancer. However, EBRT often is associated with rather severe complications, including proctitis and dysuria (1). Dysuria is one of the most frequent adverse effects of brachytherapy and EBRT in patients with prostate malignancies. Given the high prevalence and increasing incidence of prostate cancer (2), it seems essential to find an effective treatment for its treatment-related complications. Several studies have shown that cellular injury to the superficial layer of the bladder and the loss of glycos amino glycan (GAG) mucus are the main causes of dysuria during radiotherapy for prostate cancer (3). This pathogenesis is similar to that of interstitial cystitis, which is treated frequently with a mucilaginous drug known as pentosanpolysulfate sodium (Elmiron) (4). Malva species are used commonly in traditional Persian medicine (TPM) as a medicinal edible plant that provides therapeutic effects (such as anti-ulcerogenic activity) that can be attributed to its high mucilage content (5). This high level of mucilaginous material has a protective effect against injuries to mucous membranes and can relieve irritation and inflammation (6). *Malvasylvestris*L, which also is known as “Khubazi” or “Panirak” and *althea officinalis*, which also is known as “Khatmi,” are Malva species that, according to TPM books and references, are mainly prescribed for urological problems, such as dysuria (7). Recent studies have concluded that Malva has anti-inflammatory, wound-healing, anti-oxidant, and anti-cancer properties (8). Polysaccharides and flavonoids are considered the main active ingredients of the Malva flower (6). In recent years, the anti-cancer properties of flavonoids and anti-oxidants have attracted a great deal of attention (9-10). Review of ethnopharmacological and phytochemical uses of *M. sylvestris* suggested that this plant can be considered as an alternative treatment for treatment of radiotherapy-induced dysuria (11-12). Therefore, the aim of this study was to evaluate the effectiveness of this safe medicinal food for preventing radiation-induced dysuria in patients who are undergoing EBRT for prostate cancer.

2. Material and Methods

2.1. Trial design

We conducted this multi-centric, double-blind, randomized study after obtaining approval from our local ethics board and after receiving the registry code from the Iranian Registry of Clinical Trials (Registration code: IRCT2012100711026N1). Enrolment of subjects took place between April 28, 2013, and August 17, 2014, at three centers in Iran, i.e., Shohada-e-Tajrish Hospital in Tehran, Imam Khomeini Hospital in Tehran, and Namazi Hospital in Shiraz. Sixty-eight patients were randomized into two groups using four block randomization. We allocated the patients randomly to the two groups, i.e., 34 patients to the drug group and 34 patients to the placebo group. After randomization and before starting EBRT, the patients received sachets containing four grams of equally mixed *Althea officinalis* and *Malvasylvestris* or placebo powder. They were instructed to use the medication (or placebo) three times a day for six weeks. Then, the patients were selected randomly to be treated with either Malva or placebo. The primary outcomes were changes in the severity scores for dysuria and in the the Visual Prostate Symptom Score (VPSS).

2.2. Patients

All patients who were planned with EBRT with diagnosis of prostate cancer and signed informed consent and were able to express dysuria and did not have Foley catheter were enrolled in the study. Patients who were excluded from the study were patients with distant metastasis, who received chemotherapy concurrent with EBRT, who were

sensitive to the drug or the placebo, who had positive urine cultures indicative of infection, and who needed other management of their urinary symptoms, such as the insertion of a Foley catheter.

2.3. Interventions

All patients were instructed to use the medication they had been given (Malva or the placebo) three times a day for six weeks at random times. The patients and physicians were blinded to the allotted treatment, and the analysis was based on the treatment received. The patients were followed by a TPM physician every two weeks for eight weeks.

2.4. Outcome

After intervention, the patients were evaluated before EBRT and on the second, fourth, and sixth weeks after EBRT concerning the presumed primary outcome measure. Urinary function was assessed during each visit by asking questions based on the VPSS and a dysuria severity score scale 0-10 (with zero representing no dysuria and 10 being the most intense pain possible). Patients rated their symptoms and severity of dysuria only in the past 24 hours, not for the past fortnight. The scores were obtained at their first visit before EBRT and during the second, fourth, and sixth weeks after EBRT. The primary outcome was changes in the severity scores for dysuria and the Visual Prostate Symptom Score (VPSS).

2.5. Sample size

This study included 68 patients with histologically proven prostate adenocarcinoma who were intended to treat with EBRT and able to declare the severity of their dysuria. These patients were planned to take either Malva or the placebo.

2.6. Randomization

Sixty-eight patients were randomized into two groups using four block randomization. We allocated the patients randomly to the two groups: 34 patients to drug and 34 patients to placebo group. After randomization and before starting EBRT, the patients received sachets that contained four grams of equally *Althea officinalis* and *Malvasylvestris* or placebo powder that had the same shape and appearance and the same container. We chose this randomization scheme to balance the two kinds of treatment, thereby eliminating comparative bias. The patients and physicians were not aware of the kind of medications that had been selected for the patients.

2.7. Blinding

This was a double-blinded study because the kinds of medications used for the patients and the type of medication were prescribed by physicians for patients were blinded to the allotted treatment and the analysis was based on the treatment received. We tried to diminish the biases by blinding the patients, staff, and physicians.

2.8. Statistical methods

We visited the patients before EBRT and at two, four, and six weeks after EBRT. At the last visit, the VPSS and dysuria severity score were completed. The changes in the VPSS and dysuria severity score between baseline and each follow up visit were documented. The results were compared between the two groups in the study, i.e., those with Malva medication and those with placebo using repeated measures analysis of variance (ANOVA) and t-tests.

2.9. Research ethics

Sixty-four patients of the 68 patients signed informed consent forms. In addition, the ethical regulations dictated in the act provided by the Research Institute for Islamic and Complementary Medicine (RICM) (reference number of research ethics committee: 934/MT/26 P) were strictly observed.

3. Results

Of the 68 patients who registered, 60 completed the study (Figure 1). Four patients withdrew consent, one patient discontinued the placebo because the medication got stuck in his throat causing nausea and discomfort, and three others discontinued the placebo because it did not show any effects after two weeks of consumption. The median age of the 68 patients was 66 (range: 46-88), and the median ages of the placebo and Malva groups were 65 (range: 46-88) and 67 (range: 49-74), respectively. The median Gleason score in all patients was 7 (range: 3-9), and the median Gleason score of the placebo and Malva groups were 7 (range: 6-9) and 7 (range: 3-9), respectively. Fifty-five patients received hormonal therapy (24 patients in the placebo group and 31 patients in the Malva group). Thirty-nine patients were treated by radical prostatectomy and adjuvant EBRT (18 patients in the placebo group and

21 patients in the Malva group) and 21 patients were treated by definitive EBRT (10 patients in the placebo group and 11 patients in the Malva group). The median cumulative radiation doses administered as 95% isodoses to the prostate in both the placebo group and the Malva group were 70 Gy (range: 50.4-76) and 70 Gy (50.4-76), respectively. The characteristics of the patients and their treatments are summarized in Table 1.

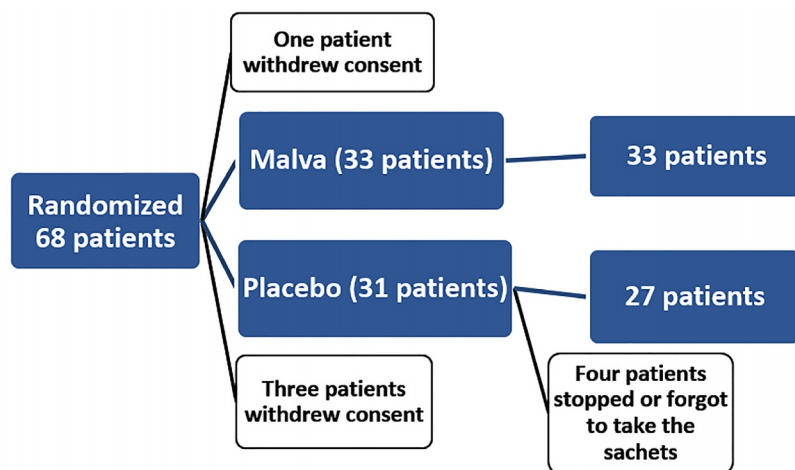


Figure 1. Diagrammatic representation of the fate of the 68 randomized prostate cancer patients

Table 1. Treatment characteristics of 60 prostate cancer patients enrolled in the study

Characteristic		All patients	Placebo group	Malva group
Number of patients		60	27	33
Age	Mean	64.6	63.56	65.45
	SD ^a	7.67	8.96	6.48
	Median	66	65	67
	Range	46-88	46-88	49-74
Prostatectomy		39	18	21
Hormonal therapy		55	24	31
Gleason score	Mean	7	7.19	6.85
	SD ^a	1.19	1	1.33
	Median	7	7	7
	Range	3-9	6-9	3-9
Total dose of Radiotherapy	Mean	68.67	68.14	69.1
	SD ^a	4.96	4.74	5.17
	Median	70	70	70
	Range	50.4-76	50.4-72	50.4-76

^aSD: Standard deviation

Twenty-one of 27 patients in placebo group (77.7%) had dysuria, while 23 of 33 patients (69.6%) who received Malva (odds ratio=2.70 for dysuria) had dysuria. The mean scale of dysuria was 2.5 in the placebo group and 1.1 in the Malva group. There were no differences between the placebo group and Malva group before EBRT based on the dysuria score ($p = 0.79$). After two, four, and six weeks of Malva treatment, dysuria due to EBRT was milder in the treatment group than in the control group, and the differences were statistically significant ($p = 0.005$, $p = 0.004$, $p = 0.001$ respectively). On the whole, dysuria due to EBRT in the Malva group compared to the placebo group had statistically significant differences ($p < 0.001$) (Table 2). Figure 2 also shows the prophylactic effect of Malva on the severity of dysuria. There were no differences between the control group and the Malva group before the start of EBRT based on the VPSS ($p = 0.43$). After two, four, and six weeks of Malva treatment, VPSS due to EBRT was lower in the Malva group than in the control group, with statistically significant differences ($p = 0.003$, $p = 0.001$, $p = 0.009$, respectively). Overall, VPSS due to EBRT in the Malva group compared to the placebo group had statistically significant differences ($p < 0.001$) (Table 2). Figure 3 also shows the prophylactic effect of Malva on VPSS.

Table 2. Mean scores of dysuria and VPSS for the 60 prostate cancer patients

Variable		Mean (SD) ^a Placebo group	Mean (SD) Malva group	p-value
Dysuria score	Before RT ^b	0.5 (0.97)	0.4 (0.90)	0.79
	After two weeks of RT	2.66 (2.51)	1.18 (1.46)	0.005
	After four weeks of RT	3.88 (2.67)	1.81 (1.74)	0.004
	After six weeks of RT	3.11 (2.70)	1.15 (1.30)	0.001
VPSS ^c	Before RT	8.4 (1.81)	8.07 (1.76)	0.43
	After two weeks of RT	11.14 (2.91)	9.19 (1.99)	0.003
	After four weeks of RT	11.87 (2.66)	9.69 (2.00)	0.001
	After six weeks of RT	10.55 (2.90)	8.69 (1.44)	0.009

^aSD: Standard deviation; ^bRT: Radiation therapy; ^cVPSS: Visual Prostate Symptom Score

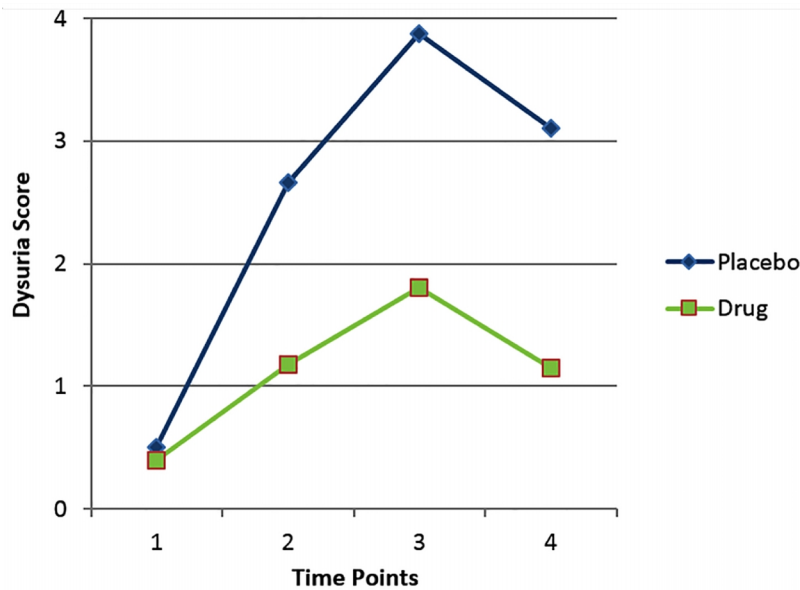


Figure 2. Prophylactic effect of Malva on the severity of dysuria

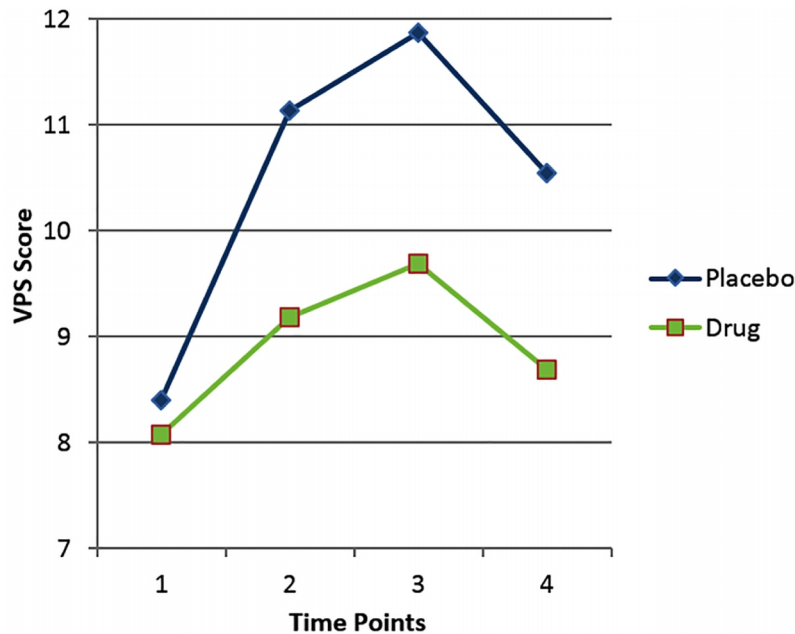


Figure 3. Prophylactic effect of Malva on VPSS

4. Discussion

EBRT causes numerous acute and long-term complications, including proctitis and dysuria. The new treatment modalities, such as 3-dimensional conformal radiation therapy (3D-CRT) and intensity-modulated radiation therapy (IMRT) can diminish those complications and lead to a better quality of life (1). Some studies have shown that older patients traditionally suffer worse side effects from EBRT because they may have a slower rate of healing (13). However, the median ages of the patients in the placebo group and the Malva group were 65 (range: 46-88) and 67 (range: 49-74), respectively, that was the similar ages for the placebo and Malva group. Some studies have shown that alfa-1 blockers, such as terazosin, have a relaxing effect on neck of the bladder neck, resulting in a better urinary function during radiation therapy (14). However, none of the 60 patients in our study received alfa-1 blockers during EBRT or within six weeks after EBRT. In contrast, anti-inflammatory drugs, such as ibuprofen, have not been proven effective in alleviating the severity of dysuria during EBRT (15). It seems that, in the management of radiation-induced urinary complications, apart from reducing the inflammation (1), dealing with the overactivity of the detrusor muscle and urethral stricture should be considered (16).

Malva species are considered to have both anti-inflammatory and spasmolytic effects (17). Moreover, they have a high content of mucilage and flavonoids (5), which explains their protective effect on EBRT-induced urothelial cell damage (3). Currently, the use of herbs to treat patients who have prostate cancer is increasing despite the fact that only a few studies have been conducted in this field. Studies on the protective effects of cranberries on the mucosal layer of the bladder (18) have shown no effect (19-20). There were some limitations in our study. First, it was a multi-centric study, so it clears that a double blind randomized clinical trial should have been done at a single institution to avoid inter-observer variations. Second, the number of patients (60) was considered small for accurate analysis of the potential protective effect of a drug in urinary toxicity induced by EBRT. Third, we did not evaluate late urinary toxicities (late cystitis) in our study.

5. Conclusions

In this multi-centric, double-blind, randomized clinical trial, it was shown that a mucilaginous herb (Malva) had a strong, protective effect in relieving the pain associated with EBRT-induced urinary toxicity. While modern radiotherapy techniques, such as 3D-CRT and IMRT, can reduce gastrointestinal and genitourinary toxicity induced by EBRT, the application of traditional Iranian herbal treatments for these side effects of modern therapies requires an intentional transfer of historical concepts to modern treatment procedures.

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Clinical Trial Registration: The study is registered in the Iranian Clinical Trial Registry Center (IRCT2012100711026N1).

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Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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