Clinical Cancer Investigation Journal-ISSN: 2278-0513

Selenium Supplementation Reduces Chemoradiotherapy-Induced Adverse Gastrointestinal Effects in Pelvic Cancer Patients

Abstract

Patients with pelvic cancer who receive radiotherapy are always going to experience side effects from the treatment. This investigation intends to employ selenium supplementation to lessen gastrointestinal symptoms (GI). Patients with pelvic cancer were separated into the control and selenium groups and received four fields of radiation. In selenium groups, patients received selenium supplementation throughout therapy, and their GI side effects were assessed using the National Cancer Institute score. For evaluating the side effects and the degree of significant correlation, odds ratios (OR) and p-values lower than 0.05 were employed. Results revealed that among patients who didn't receive selenium, the risk of diarrhea in higher grades is higher than in lower grades, with the rate of grades II, III, and 0 having an OR=3.6 and a p-value: 0.004. Tenesmus and vomiting had OR values of 0.16 and 0.79, respectively, with a p-value of 338 and 0.21 for each. The outcomes of radiation and quality of life in patients with pelvic cancer were both improved by selenium supplementation, according to the results given here.

Keywords: *Selenium, Pelvic cancer, Radiotherapy, Side effects, Mitigation*

Maryam Bahador[1], Saeed Rajaee[2], Saiedeh Mahmoodzadeh[3], Mohammad Hasan Larizadeh[4]

Corresponding author: Saeed Rajaee

1) ma.bahador@kmu.ac.ir
2)Saidraha2000@yahoo.com
3)Sa.mahmoodzadeh75@gmail.com
4)Mh.larizadeh@kmu.ac.ir
1,2,4: Department of Radiation Oncology, Kerman University of Medical Sciences, Kerman, Iran
3: MSc in Epidemiology, School of Public Health, and Physiology Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran

Introduction

Pelvic malignancies (PM) are common diseases among men and women worldwide (1). One of the most popular and successful therapies for PMs is radiotherapy (2). Studies have indicated radiation-induced several adverse effects during or after pelvic radiotherapy (3). Although technical advances in dose delivery approaches such as intensity-modulated radiotherapy and volume-modulated arc therapy have resulted in more treatment outcomes, concerns remain (4).

For years, radiation protectors and mitigators have been used to alleviate radiotherapy-induced normal tissue injuries (5-8). Herbal, natural, chemical, and mixed compound radiation modifiers are tested clinically or in animal studies and feasible results have been obtained (9). For radiotherapy-associated pelvic disorders, a wide range of studies has focused on probiotics, melatonin, bacterial compounds, and famotidine to reduce bowel diseases and other pelvic normal tissues (10).

Selenium supplements are frequently used in cancer patients. Selenium has long been recognized as a crucial trace element that plays a role in human redox control and antioxidant defense (11). Selenium has been researched as a treatment for radiotherapy-related side effects because radiation side effects have been connected to oxidative cell damage in the human body. Some previous studies have demonstrated that selenium reduces radiation-induced diarrhea, dysphagia, xerostomia, stomatitis, and loss of taste (12). On the other hand, a wealth of data has indicated that selenium has a great role in cancer induction and treatment (13).

The presented study aimed to evaluate the effects of selenium supplementation in patients with pelvic malignancies undergoing chemo/radiotherapy. In this study, we investigated the effects of selenium to reduce chemo/radiation-induced gastrointestinal (GI) and urinary complications.

Materials and Methods

Patients

The current study used block randomization as a parallel interventional design. We created blocks with a 4 cell size for randomization, 20 blocks were chosen at random, and 40 patients were assigned to each group. No patients were lost to follow-up during the study, and all patients received the prescribed intervention (Fig 1). The study was conducted as prospective and between September 2017 and September 2018, all pelvic cancer patients undergoing chemo/radiotherapy were included in the study. Patients were randomly assigned into two main groups: 1) Se-group: patients who have administrated selenium supplementation and 2) Control-group: patients who were not administrated selenium supplementation. Prior to the experiment, all patients provided written informed consent, which was approved by the Kerman University of Medical Sciences' regional ethics committee This study was in accordance with the Helsinki Declaration. All patients were treated with four fields with a dose of 50-70 Gy (mean dose = 60 Gy) in 20-30 fractions. All 3DCRT plans were generated using the ISOGRAY system. The chemotherapy regimen was done by Capecitabine (Commercial: Xeloda) for rectum and Cisplatin for cervix and bladder cancers.

Patients with baseline GI and urinary diseases were excluded from the study.

The patients in the Se-group were administered 200 μg sodium during the treatment course. Sodium was taken as an oral fluid one hour before the radiotherapy was performed. The control groups received just radiotherapy and distilled water as a placebo without any selenium intake.

Adverse effects assessment

Each patient was investigated clinically at baseline, during, and weeks after the end of radiotherapy. The adverse effects including diarrhea, vomiting, and tenesmus were evaluated according to the national cancer institute (NCI) scale.

Statistical analysis

The STATA software was used for all statistical analysis. Analysis was carried out with the goal of treatment in mind. To determine the association between unfavorable effects and the linear model parameters, a generalized estimating equation (GEE) was used. A significant correlation was defined as a P-value of less than 0.05. In order to measure the strength of the relationships, the odds ratio (OR) was calculated.

Results

80 patients with a median age of 60y (40-80) were divided randomly into two groups. Baseline characteristics were not different between the two groups (table 1). Mean ± SD of age was **59.5 ± 12.8** and **63.8 ± 11.2** in the intervention and placebo groups respectively (p= 0.11). The mean ± SD of BMI was **22.9 ± 4.7** and **22.9 ± 3.5** in the intervention and placebo groups respectively (0.98). 20 (50%) individuals in the intervention and 12 (30%) individuals in the control group were female (p= 0.067). all individuals in the intervention and control groups were married.

Results for chemo/radiation-induced diarrhea for different grades were shown in table 2. These results are the comparison of diarrhea between the control and Se groups. The rate of this consequence among patients who did not get selenium is higher in higher grades than in lower grades, as was seen.

Tenesmus and vomiting had OR values of 0.16 and 0.79, respectively, with a p-value of 338 and 0.21 for each. Table 3 provides results for different problems.

Chemoradiotherapy is an effective treatment approach for managing pelvic malignancies. But these patients suffer from GI and urinary complications due to radiation and chemical agents. In this study, we investigated the radiomitaigative effects of selenium supplementation in pelvic malignancy patients undergoing chemoradiotherapy. Our results showed that some GI adverse effects such as diarrhea were significantly reduced in patients who received Se.

Selenium is studied as a critical agent for cancer prevention/progression, infection, and infertility and also as a mitigator to reduce adverse effects of radiation treatment. Several mechanisms have been suggested for selenium-induced cancer prevention and radiation protection (14). Some studies have revealed that selenium reduces oxidative damage and can limit DNA damage (7). Additionally, some studies revealed that selenium triggers a number of enzyme pathways that are involved in the blockage of the cell cycle to allow DNA repair, inhibition of angiogenesis, improvement of the immune response, induction of apoptosis in the cancer cell, increase in the tumor-suppressor protein p53, changes in DNA methylation, and inactivation of protein kinase C (PKC). Selenium is also used as a complementary alternative medicine in patients with prostate and lung cancer (12).

Our results also showed that selenium could significantly reduce skin burn and pain in pelvic cancer patients undergoing radiotherapy. Skin burn is a routine adverse effect in radiotherapy patients. Based on these results, we could suggest using selenium as a vital factor for reducing radiation burn in different cancer patients. Also, selenium reduced other complications such as abdominal cramps and dysuria.

According to earlier research, there is no set dose, duration, cancer type, duration, or side effect regimen for selenium supplementation. Puspitasari et al. reviewed studies and selenium applications in radiotherapy and came to the conclusion that supplementing with selenium at high doses and for an extended period of time is risky due to selenium toxicity. They found that selenium improves quality of life, reduces radiotherapy side effects, and doesn't affect the effectiveness of radiotherapy at doses between 200 and 500 μg/day.

Despite the importance of our findings, this study has a number of flaws. Initially, the total number of patients. In our cross-sectional prospective study, this amounts of patients are low, and more patient data are needed. This study could be verified by more human data. Second, there is some issue that induces bias in the study such as chemotherapy, different dose regimen and fractionation, different cancer types, and patient characteristics.

Table 1. Bassline characteristic on patients

		Control	Se-group	p
gender	**Male**	**28 (70)**	**20 (50)**	
	Female	**12 (30)**	**20 (50)**	**0.068**
Opium	**Yes**	**20 (50)**	**14 (35)**	
	No	**20 (50)**	**26 (65)**	**0.17**
age	**≤70**	**30 (75)**	**32 (75)**	

	>70	**10 (25)**	**8 (20)**	**0.59**
Drug type	**no chemotherapy**	**30 (75)**	**24 (60)**	**0.12**
	chemotherapy	**2 (5)**	**8 (20)**	
	therapy/chemotherapy	**8 (20)**	**8 (20)**	
marital	**Married**	**40 (100_**	**40 (100)**	**-**
	Single	**0**	**0**	
continuous				
variables		**Control Mean ± SD**	**Se-group Mean ± SD**	
BMI		**22.9 ± 3.5**	**22.9 + 4.7**	**0.98**
age		**63.8 ± 11.2**	**59.5 ± 12.8**	**0.11**

Table 2. Results on chemo/radiation induced diarrhea for different grades

Grades comparison	**OR**	**P-Value**
Grade II , III to Grade 0	3.6	0.004
Grade II , III to Grade I	2.3	0.004
Grade I to Grade 0	1.7	0.004

Table 3. Results on chemo/radiation induced other complications

Grades comparison	OR	P-Value
Pain	0.56	0.02
Abdominal cramp	0.16	0.5
Skin burn	2.08	0.01
Dysuria	0.83	0.5

Conclusion and Final Results

The results presented here indicated that selenium supplementation could reduce gastrointestinal complications including diarrhea and improve quality of life and radiotherapy outcomes in pelvic cancer patients. The authours recommend by this study should be do investigation by large numbers of patient with cancer that they recive selenium with concurrent radiotherapy to evaluate side effect of radiation.

Acknoledgment

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest, in the subject matter or materials discussed in this manuscript.

Also there is no conflict between authors.

This study was approved by the local ethics commitee of Kerman University of Medical Science and written informed consent was obtained from all patients before experiment.

References

1. Kroon HM, Collaborative P, Kroon H, Dudi-Venkata N, Bedrikovetski S, Thomas M, et al. Palliative pelvic exenteration: A systematic review of patient-centered outcomes. European Journal of Surgical Oncology. 2019.

2.Morris KA, Haboubi NY et al. Pelvic radiation therapy: Between delight and disaster. World journal of gastrointestinal surgery. 2015;7(11):279.

3. Handa E, Puspitasari IM, Abdulah R, Yamazaki C, Kameo S, Koyama H, Recent advances in clinical studies of selenium supplementation in radiotherapy. Journal of Trace Elements in Medicine and Biology. 2020;62, 127-145.

4. Douglus A et al, Handbook for Principles and Practice of Gynecologic Oncology. LWW publisher, 3th edition, 2021; 46-82.

5. Halperien M.D. et al., Perez and Brady's Principles and Practice of Radiation Oncology. Lippincott Williams & Wilkins; 7th edition, 2019; chapter 29; 592.

6. Saadipoor A, Razzaghdoust A, Simforoosh N, Mahdavi A, Bakhshandeh M, Moghadam M, et al. Randomized, double-blind, placebo-controlled phase II trial of nanocurcumin in prostate cancer patients undergoing radiotherapy. Phytotherapy research. 2019;33(2):370-8.

7. Jain V, Singh GN et al.. Study Of Copper, Zinc And Selenium Associated With Superoxide Dismutase, Catalase And Glutathione Peroxidase Level In Serum Of Breast Cancer Patients Of North India. Journal of Cancer Research & Therapeutics. 2017;13.

8. Farhood B, Mortezaee K, Motevaseli E, Mirtavoos-Mahyari H, Shabeeb D, Eleojo Musa A, et al. Selenium as an adjuvant for modification of radiation response. Journal of cellular biochemistry. 2019.

9. Muecke R, Micke O, Schomburg L, Buentzel J, Kisters K, Adamietz I. et al. Selenium in radiation oncology-15 years of experiences in Germany. Nutrients. 2018;10(4):483.

10. Elango S, Samuel S, Khashim Z, Subbiah U. et al. Selenium Influences Trace Elements Homeostasis, Cancer Biomarkers in Squamous Cell Carcinoma Patients Administered with Cancerocidal Radiotherapy. Asian Pacific journal of cancer prevention: APJCP. 2018;19(7):1785.

11. Maiyo F, Singh M. et al. Selenium nanoparticles: potential in cancer gene and drug delivery. Nanomedicine. 2017;12(9):1075-89.

12. Cruz LY, Wang D, Liu J. et al. Biosynthesis of selenium nanoparticles, characterization and X-ray induced radiotherapy for the treatment of lung cancer with interstitial lung disease. Journal of Photochemistry and Photobiology B: Biology. 2019;191:123-7.

13. Puspitasari IM, Abdulah R, Yamazaki C, Kameo S, Nakano T, Koyama H. et al. Updates on clinical studies of selenium supplementation in radiotherapy. Radiation Oncology. 2014;9(1):125.

14. Puspitasari IM, Yamazaki C, Abdulah R, Putri M, Kameo S, Nakano T, et al. Protective effects of sodium selenite supplementation against irradiation-induced damage in non-cancerous human esophageal cells. Oncology letters. 2017;13(1):449-54.