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Practical treatment approach of radiation induced cystitis

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A B S T R A C T

Objective: Establish a pattern of behavior and treatment algorithm at the onset of hematuria in patients with a previous history of pelvic radiation, checking for this different treatment options reflected in the literature.

Material and methods: Through performing a PubMed literature review of articles related to IC lies, searching items includes the different treatment options: intravesical hyaluronic acid, conjugated estrogens, pentosan polysulfate, oral aminocaproic acid, recombinant factor VIIa, hyperbaric chamber, embolization, aluminum intravesical, Helmstein ball and formalin. Limits the search to English or Spanish publications and excluding those related to animal experimentation.

Results: Every option is exposed, referring to the physiopathology, dosage regimen and administration, side effects and treatment efficacy.

Conclusions: Once patient hemodynamic stabilization is achieved, and after ruling out bladder tumors injuries and /or haematuria originating from the upper urinary tract, treatment should start rolling. Knowing different treatment options and patterns of administration will allow the urologist to obtain a higher rate of success in the difficult management of this condition.

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Guía práctica para el manejo y tratamiento ante la cistitis radical

R E S U M E N

Palabras clave:

Cistitis r dica

Hematuria

Radioterapia

C ncer de pr stata

Gu a de tratamiento

Objetivo: Establecer una pauta de actuaci n y un algoritmo terap utico ante la aparici n de hematuria en pacientes con antecedentes de radioterapia p lvica, revisando para ello las diferentes opciones de tratamiento reflejadas en la literatura m dica.

Material y m todos: A trav s de PubMed se realiza una revisi n bibliogr fica de art culos relacionados con la cistitis r dica, incluyendo t rminos de b squeda referidos a las diferentes opciones de tratamiento:  cido hialur nico endovesical; estr genos conjugados, pentosan polisulfato,  cido aminocaproico oral, factor VIIa recombinante, c mara hiper-

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bárica, embolización, aluminio endovesical, balón Helmstein y formolización. Se limita la búsqueda a publicaciones en castellano e inglés y se excluyen aquellas referidas a la experimentación animal.

Resultados: Se expone cada una de las opciones citadas, haciendo referencia al mecanismo de acción, pauta y dosis de administración, efectos secundarios y prevención de los mismos si es posible así como eficacia del tratamiento.

Tras conseguir estabilizar hemodinámicamente al paciente y descartar la presencia de lesiones neoformativas vesicales y/o hematurias originadas en tramo urinario superior, se debe iniciar un tratamiento escalonado.

Conclusiones: El conocer diferentes opciones de tratamiento y sus pautas de administración permitirá al urólogo obtener una mayor tasa de éxitos en el difícil manejo de esta patología.

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Introduction

When the bladder is exposed to radiation during radiotherapy for cancer in pelvic structures, a number of histopathologic changes develop which have clinical repercussions. In addition to the urinary irritative syndrome characterized by urgency, pollakiuria, and dysuria, the development of hematuria of variable severity is one of the most difficult complications that the urologist must manage.

With the purpose of facilitating the practical urological management of radiation-induced cystitis, this article briefly reviews the therapeutic options available.

The objective of this study is to establish directives and a diagnostic algorithm to facilitate the management of these patients.

Material and methods

A bibliographic search was done in PubMed for articles about radiation-induced (actinic) cystitis. The search terms include those referring to the various treatment options: systemic, intravesical treatment and/or physical procedures. They are: Intravesical hyaluronic acid, conjugated estrogens, pentosan polysulfate, oral aminocaproic acid, recombinant factor VIIa, hyperbaric chamber, embolization, intravesical aluminum, Helmstein balloon, and formalin instillation. The terms radiation, radiation-induced and actinic were also entered in the search engine.

No comments are made regarding the date or medium of publication.

The search was limited to articles in Spanish and English, and animal experiments were excluded.

For each therapeutic option, the scientific level of evidence according to the current classification published in the clinical practice guidelines of the European Association of Urology is given:

Ia: Evidence obtained from meta-analysis of well-designed controlled, randomized trials.

Ib: Evidence obtained from at least one controlled randomized trial.

IIa: Evidence obtained from at least one well-designed controlled study without randomization.

IIb: Evidence obtained from at least one well-designed quasi-experimental study.

III: Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies, or case and control studies.

IV: Evidence obtained from expert committee reports or opinions, or clinical experience of respected authorities.

Anatomopathological considerations

The histopathologic changes associated with radiation exposure occur in two phases: acute and chronic. The acute and subacute phases occur within 3-6 months after therapy. The histological examination of the tissue shows urothelial desquamation, atypia, and eosinophilic infiltration.¹ The condition manifests clinically as urinary urgency, dysuria, and/or pollakiuria. Gross hematuria occurs in 7.7% of patients and although it is more common between 6 months and 5 years after treatment^{3,5} this interval can extend from the first 6 weeks to up to 14 years later.² The chronic phase begins 6 months after radiotherapy. The effect of radiation on the bladder wall is ischemia leading to vascular and muscle changes. The vascular endothelial injury causes hyperplasia, occlusion, and perivascular fibrosis. The muscle injury causes the substitution of smooth muscle fibers with fibroblasts, which leads to fibrosis and the resulting decreased bladder capacity and compliance.¹ Both alterations increase the bladder's susceptibility to mucosal ulceration and hemorrhage, and even perforation and fistula formation.²

Patient evaluation

Patients suffering from radiation cystitis can present with a range of clinical manifestations, from asymptomatic microscopic hematuria to gross hematuria with clots and subsequent urine retention. Even when a preliminary diagnosis is made based on the patient's context, infection and bladder cancer must be ruled out.

A urinary infection may exacerbate the hematuria caused by radiation cystitis.

Radiation therapy for ovarian or uterine cervical cancer increases the risk of bladder cancer 2- to 4-fold; men undergoing radiotherapy for prostate cancer have a 50% increased risk of bladder cancer.³ An urethrocystoscopy and/or urine cytology are mandatory to rule out bladder cancer when episodes of gross hematuria are present. Endoscopy also permits intraluminal visualization and shows the characteristic vascular neoplastic formations.

If hematuria persists after continuous bladder lavage and intravesical coagulation of bleeding lesions, hemodynamic stabilization must be achieved. Once the patient is stable, the most appropriate option should be chosen from the several available at each hospital.

Treatment options

There is no definitive treatment for severe hemorrhagic cystitis. Rather, there are several treatment options available in multiple combinations.⁴ The most commonly used approaches are detailed below, with brief comments on their administration, efficacy, and potential side effects.

Intravesical treatment

1. Intravesical hyaluronic acid
2. Intravesical aluminum
3. Bladder formalin instillation

Systemic treatment

4. Conjugated estrogens
5. Pentosan polysulfate
6. Oral aminocaproic acid
7. Recombinant factor VIIa

Physical procedures

8. Hyperbaric chamber
9. Embolization of the internal iliac arteries
10. Distention with Helmstein balloon
11. Cystectomy

Intravesical treatments

1. Hyaluronic acid

Intravesical hyaluronic acid temporarily restores the deteriorated glycosaminoglycan layer of the luminal surface of the bladder wall, stimulates the replacement of connective tissue, and later facilitates the nesting and recovery of epithelial cells.

It is widely accepted for interstitial cystitis^{5,6} and has been proposed as a complementary preventive treatment for repeat urinary infections and radiation bladder disease.⁷

After emptying the bladder, 40 mg of the product diluted in 50 mL of saline solution are instilled; the patient retains the solution for at least 30 min. Instillations are repeated once a week during the first month, and subsequently once a month until symptoms disappear.

Level of evidence: III.

2. Irrigation with aluminum salts

Aluminum (either aluminum ammonium sulfate, aluminum hydroxide, or aluminum potassium sulfate) works by the astringent action of protein precipitation at the cell surface and interstitial spaces.⁸ This leads to decreased capillary permeability, contraction of the intercellular space, vasoconstriction, hardening of the capillary endothelium, and reduction of edema, inflammation, and exudate.⁹

After removing vesical clots, an irrigation is initiated with 5 L of distilled water in which 50 g of aluminum (1%) have been dissolved, at a rate of 250-300 mL/h.

This technique is safe, effective, and generally well tolerated.¹⁰ Side effects include suprapubic pain and spasms during instillation,⁹ aluminum toxicity complications, and allergic reactions to aluminum salts. Aluminum toxicity may occur in patients with renal impairment and/or a large absorptive bladder surface. The development of lethargy, confusion, metabolic acidosis, or elevated aluminum concentration mandates cessation of treatment.¹¹

Level of evidence: III.

3. Formalin instillation

Intravesical formalin instillation was described by Brown¹² in 1969 as a method of controlling hematuria caused by advanced carcinoma of the bladder. Despite success rates of more than 80%, the potential side effects and complications restrict the use of this treatment.

Toxicity depends directly on the concentration of formalin used, and to a lesser extent, on the duration of the exposure.¹³ The series published show very variable aspects of this technique.

Toxicity can be local or systemic by absorption and metabolism to formic acid and formate. It includes: reduced bladder contractility, incontinence, ureterovesical obstruction, ureteric strictures, acute tubular necrosis, vesico-ileal and vesicovaginal fistulas, rupture of the bladder, and toxic effect on the myocardium.¹¹

After excluding vesicoureteral reflux with cystography (or preventing reflux with a Fogarty catheter) and evacuating clots from the bladder, the following recommendations can be used to proceed:³⁵ with the patient under epidural or general anesthesia, the genital areas (skin and mucosa) should be protected with Vaseline and/or the vagina packed to prevent abrasion from leaked instillation solution. The irrigation should be initiated at a low concentration (1-2%) and increased as necessary; the duration should not exceed 15 minutes, and the intravesical pressure should be under 15 cmH₂O.

Due to the potential complications, this method should be used only when more conservative measures have failed.

Level of evidence: IV.

Systemic treatments

4. Conjugated estrogens

The mechanism through which conjugated estrogens act on hemorrhagic cystitis is not well understood. Accepted hypotheses are a modulating effect on cellular immune response and cytokines, and the stimulation of endothelial cell activity.¹⁴ Success^{15,16} as well as failure¹⁷ have been reported in literature regarding the use of this method for the treatment of hemorrhagic cystitis. Its relative low cost, few side effects, ease of administration, and the fact that it does not compromise subsequent treatment options mandate that this method be considered among frontline treatments.

The administration of estrogen has been associated with hypercoagulability¹⁸ and hepatotoxicity, therefore liver enzymes and serum bilirubin should be determined before initiating this treatment.

The regimen described by Ordemann et al¹⁹ consists of beginning with 6 mg/d divided in 3 doses, increasing gradually to up to 12 mg/d and/or control of hematuria. Hematuria was reported to resolve between just 8 h and 7 days after administration. Treatment is extended over 5-16 weeks with decreasing doses of conjugated estrogens.

Level of evidence: IV.

5. Sodium pentosan polysulfate

Up to 5% of the administered sodium pentosan polysulfate is excreted in urine.²⁰ Although the exact mechanism of action is not known, it repairs the layer of glycosaminoglycans in the urothelium and has an anti-inflammatory effect.²¹ Few studies have been published regarding the use of this substance; small series with long-term follow-ups support the efficacy of the treatment.^{22,23} The low number of side effects, the absence of interaction with other treatments, and the relative rapidity of results (1-8 weeks)²⁴ make this a substance that must be considered a frontline treatment.

Level of evidence: IV.

6. Aminocaproic acid

Several authors have reported the use of epsilon aminocaproic acid for the management of bladder hemorrhage, with different success rates. Stefani et al²⁵ described the oral administration at a dose of 150 mg/kg/d for 21 days as an effective management of hematuria in nine patients, with no side effects. Singh et al²⁶ have proposed it as a safe and effective therapy in 37 patients.

Regardless of the route of administration, prior exclusion of blood dyscrasias is mandatory. This therapy must be used with caution due to the short duration of the studies and the lack of continuity of use.

Level of evidence: IV.

7. Recombinant factor VIIa

Recombinant factor VIIa promotes the formation of the fibrin clot at the site of vascular injury, forms a complex with the exposed tissue factor, and acts on activated platelets.²⁷ It has been approved for intractable hemorrhage in patients with factor VIII and IX inhibitors, factor VII deficiency, and Glanzmann's thrombasthenia. It has been effective for thrombocytopenias and platelet defects, bleeding associated with oral anticoagulant therapy, severe trauma, and impaired liver function,²⁸ as well as for severe bleeding in adults without congenital coagulopathy or inhibitor development.²⁹

Few randomized clinical trials have been published about the many uses of the product; most publications are clinical notes with small samples. Scarpelini and Rizoli published a review where they note the use of the substance in various surgical specialties, and point out a decrease in preoperative blood loss during retropubic radical prostatectomies after administering 20-40 µg/kg of rFVIIa;³⁰ however, the blood losses in the control group were considerably higher than what is accepted for that surgery.

Successful use in gynecology for hemorrhagic cystitis after radiation therapy when all other measures had failed has been reported.³¹

Candidates to treatment with rFVIIa must meet the following hematologic criteria:³² hematocrit more than 24%; fibrinogen 50-100 mg/dL; platelets >50,000×10⁹; pH >7.2; furthermore, the administration of the product must comply with certain clinical guidelines.³³

The request for recombinant factor VIIa for the treatment of radiation cystitis falls within the framework of "compassionate use". The recommended dose is 90 µg/kg; a second dose can be administered after 20 min if success is not achieved. The administration of more doses has not shown to be effective.

Level of evidence: IV.

Physical procedures

8. Hyperbaric chamber

The administration of high pressure oxygen stimulates angiogenesis in the radiation-damaged tissue.³⁴ Sessions last on average 90 minutes and administer 100% oxygen in chambers at 2-2.5 atm of pressure.³⁵ Sessions take place once a day, five days a week. The number of sessions varies depending on the series, but a minimum 15 to a maximum 60 is recommended before considering other therapeutic options.³⁰⁻³² In the series described, patients received an average of 30 sessions. Initiating treatment within the 3 months after the onset of hematuria yields a higher rate of success and reduces the number of sessions required.^{18,19} Prior intravesical treatments do not affect the rate of success of hyperbaric therapy.¹⁹ Treatment is well tolerated; the complications reported are isolated cases of ear and eye barotrauma.

Level of evidence: IIb.

9. Arterial embolization

Therapeutic embolization to control bladder hematuria was described in 1974 by Hald et al, who occluded the internal iliac artery.³⁶

The interruption of blood flow has a success rate close to 90%, according to the literature.³⁷ The level of the occlusion has been refined since the first embolization of the internal iliac artery to involve the anterior branch of the internal iliac, the superior and inferior vesical branches, and finally the small vessels irrigating specific regions (superselective).³⁸ Superselective embolization is associated with fewer complications.

The most common complication is gluteal pain (buttock claudication) that occurs when the superior gluteal artery is accidentally embolized when performing the procedure on the internal iliac artery. Other complications include lower extremity necrosis due to migration of the occlusive material, bladder wall necrosis, and rarely, lower extremity paraplegia attributed to the embolization of the spinal arteries with subsequent compromise of the spinal cord.³⁹

The advantages of this method are that it can be done under local anesthesia and it does not compromise subsequent treatments (figs. 1 and 2).

Level of evidence: IV.

10. Distension with the Helmstein balloon

In 1966, Helmstein successfully used hydrostatic pressure to treat bladder tumors by inducing compression tissue necrosis in 27 of 35 patients.⁴⁰ He later proposed using the same method to control hematuria.

Published articles about this therapy are mostly prior to 1980. In general, the technique is described as useful, simple, with few side effects, but with a temporary effect.

The technique consists of attaching a specially designed balloon (a balloon or condom may be used) to the sectioned end of a No. 18 Foley catheter. Under epidural anesthesia (in order to achieve bladder atonia), the device is inserted

through the urethra into the bladder. The balloon is expanded with saline solution until a pressure 10 to 25 cmH₂O over the diastolic pressure is reached.¹⁸ The pressure is maintained for 6 hours. Helmstein recommended the subsequent administration of mannitol to treat the meatal edema caused by compression, but this practice has not shown an added value in other series.⁴¹ The hemostatic effect continues for an average of 6 months.⁴²

The most frequently described complication is bladder rupture, manifesting as a sudden change in intravesical pressure during the procedure; it is always managed conservatively with urethral catheterization.

Level of evidence: IV.

11. Cystectomy

Surgery should be considered only after the above options have failed.

Anatomical dissection may be difficult due to the effects of radiation and the time elapsed since then. The type of urinary bypass used must be appropriate for each patient's characteristics, his or her degree of autonomy, the base pathology, and the prognosis. Before embolization was possible, the ligation of the hypogastric arteries was another option.

Proposed algorithm

When hematuria develops in patients who underwent pelvic radiation therapy, bladder neoplasm and hematuria from the upper urinary tract must be ruled out.

When hematuria is attributed to radiation cystitis, progressive treatment should be initiated after the hemodynamic stabilization of the patient, if required.

Formalin instillation should be considered only in life-threatening situations when surgery is contraindicated.

We propose the following therapeutic regimen:

Hematuria

Mild:

- Urethrocystography
- Intravenous urography/CT scan
- Urine sediment/Cytology
- Bladder biopsy
- Initiate ambulatory hyaluronic acid instillations
- Program hyperbaric chamber

Anemia-inducing

Urethrocystography in the operating room: evacuation of clots, electrocauterization of suspicious areas, and biopsies.

Program hyperbaric chamber

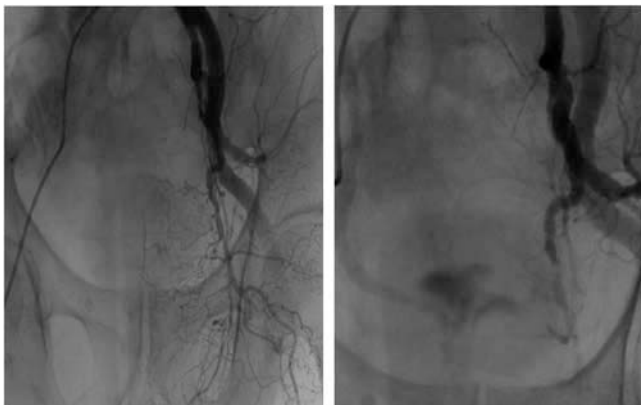
Oral treatment:

Pentosan polysulfate

Conjugated estrogens

Aminocaproic acid

Intravesical instillations: aluminum salts.



Figures 1 and 2 – Superselective embolization with fibrin plugs.

↓
Embolization
↓
Helmstein balloon
↓
Formalin instillation
↓
Cystectomy

Conclusions

We have briefly reviewed most available treatment options. There is no one single or ideal treatment. Familiarity with the various options and administration regimens will allow urologists to attain a higher rate of success in the difficult management of these patients.

Conflict of interest

The authors state that they have no conflicts of interest.

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