Practical treatment approach in radiation-induced cystitis


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ABSTRACT

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 rule out bladder tumors injuries and/or haemathuria originating from the upper urinary tract, treatment should start rolling. To know 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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Introduction

When the bladder is exposed to radiation in the context of radiotherapy for pelvic tumors, a series of histopathological changes are induced that in turn have clinical consequences. In addition to irritative micturition syndrome characterized by micturition urgency, pollakiuria and dysuria, the appearance of hematuria of highly variable intensity represents one of the most complex complications which the urologist must deal with.

The present article offers a succinct review of the available treatment options for radiation-induced cystitis, with the purpose of facilitating its practical management on the part of the urologist.

Specifically, the aim of the study is to establish an intervention protocol and define a diagnostic algorithm capable of facilitating patient management.

Material and methods

A PubMed literature search was made of articles related to actinic or radiation-induced cystitis. The search keywords included those referred to the different treatment options: systemic, endovesical and/or physical treatment procedures. These comprised the following: endovesical hyaluronic acid, conjugated estrogens, pentosan polysulfate, oral aminocaproic acid, recombinant factor VIIa, hyperbaric chamber, embolization, endovesical aluminum, Helmstein balloon and formalinization. The terms actinic and radiationinduced were also introduced in the search engine.

No limits were applied in terms of the date of publication or the publication medium.

The search was limited to publications in Spanish and English, and animal experimentation studies were excluded. The level of scientific evidence was added corresponding to each of the options according to the current classification, published in the clinical practice guides of the European Association of Urology (EAU):

Ia: The evidence comes from metaanalyses of well designed, randomized, controlled trials.
Ib: The evidence comes from at least one randomized, controlled trial.
IIa: The evidence comes from at least one well designed, nonrandomized, controlled trial.
IIb: The evidence comes from at least one well designed, quasi-experimental study.
IIl: The evidence comes from well designed, non-experimental descriptive studies such as comparative studies, correlation studies or case-control studies.
IV: The evidence comes from documents or opinions of expert committees, or clinical experiences of authorities of prestige.

Histopathological considerations

The histopathological changes after radiation exposure occur in two phases: acute and chronic. The acute and subacute phases are observed between 3-6 months after treatment. Histopathologically, urothelial desquamation, atypias and eosinophilic infiltrates have been described. Clinically, patients may experience micturition urgency, dysuria and/or pollakiuria. Macrohematuria is observed in 7.7% of the cases, and although it is more frequent between 6 months and 5 years after treatment, this interval can be expanded from 6 weeks to 14 years.

The chronic phase in turn begins 6 months after radiotherapy. The effect of radiation upon the bladder wall leads to ischemia, which in turn conditions changes at vascular and muscle level. Vascular endothelial damage causes hyperplasia, occultation and perivesical fibrosis. Muscle damage in turn causes smooth muscle fiber replacement by fibroblasts, leading to fibrosis and a secondary reduction in bladder capacity and compliance. Both alterations increase bladder susceptibility to mucosal ulceration and bleeding, and even bladder perforation and the formation of fistulas.

Patient evaluation

Patients with radiation-induced cystitis can develop clinical manifestations ranging from asymptomatic microhematuria to macrohematuria with clots and secondary urinary retention. Despite the establishment of a presumed diagnosis on the basis of the patient condition, it is always necessary to discard possible infections and/or bladder neoplasms.

Urinary infection can exacerbate hematuria produced in the context of radiation-induced cystitis.

Radiotherapy for ovarian or cervical cancer increases the risk of cardiovascular changes 2- to 4-fold, and males subjected to radiotherapy for prostate cancer have a 50% increased risk of developing bladder cancer. The exclusion of bladder neof ormations based on urethrocystoscopy and/or urinary cytology is mandatory in cases of macroscopic hematuria. Endoscopy moreover offers an endoluminal view with characteristic vascular neof ormation images.

If hematuria persists despite continuous bladder irrigation and endovesical coagulation of the bleeding lesions, hemodynamic stabilization of the patient is the objective to be pursued. With the patient under stable conditions, the management best suited to each individual case should be considered, among the range of options available in each center.

Treatment options

There is no definitive treatment for severe hemorrhagic cystitis. A number of management options must be considered, and there is a range of possible combinations. The most widespread management options are indicated below, with a brief comment on their form of administration, efficacy and possible side effects.

Intravesical treatment

1. Intravesical hyaluronic acid
2. Intravesical aluminum
3. Bladder formalinization

Systemic treatment

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

Physical measures

8. Hyperbaric chamber
9. Internal iliac artery embolization
10. Helminth balloon distension
11. Cystectomy

**Intravesical treatments**

1. **Hyaluronic acid**

Intravesical hyaluronic acid temporarily restores the deteriorated glycosaminoglycan layer of the luminal surface of the bladder wall, stimulating connective tissue replacement and subsequently facilitating epithelial cell nesting and reconstitution. Its use is widely accepted in interstitial cystitis and has been proposed as preventive cotreatment in recurrent urinary infections and in radiation-induced bladder disorders.

After bladder voiding, 40 mg of product are instilled in 50 ml of physiological saline solution – the patient being required to retain it for at least 30 minutes. The instillations are repeated once a week for the first month and then once monthly until symptoms control is achieved.

Evidence level: III.

2. **Irrigation with aluminum salts**

Aluminum (as aluminum ammonium sulfate, aluminum hydroxide or as aluminum potassium sulfate) exerts a protein precipitate astringent effect on the cell surface and in the interstitial spaces. Such irrigation results in diminished capillary permeability, contraction of the intercellular space, vasoconstriction, hardening of the capillary endothelium and a reduction of the edema, inflammation and exudate.

After extracting the possible bladder clots, irrigation is started with 5 liters of distilled water in which 50 g of aluminum are dissolved (1%), at a rate of 250-300 ml/hour.

This technique is safe, effective and generally well tolerated. Side effects have been reported such as suprapubic pain and spasms during the instillations, as well as complications derived from the toxicity of aluminum, and allergic reactions to its salts. Aluminum toxicity may be seen in patients with renal failure and/or extensive damaged bladder surfaces that act as absorbing areas. The appearance of lethargy, confusion, metabolic acidosis or plasma aluminum elevations requires treatment suspension.

Evidence level: III.

3. **Formalinization**

Intravesical formalinization or formalin instillation was described by Helminth in 1969 as a method for controlling hematuria secondary to advanced bladder carcinoma. Despite reported success rates of over 80%, the potential side effects and complications of this procedure have limited its use.

The toxicity of formalinization is directly dependent upon the concentration of the formalin employed, and to a lesser extent on the duration of exposure. The data reported in this sense in the literature are highly variable.

Toxicity is both local and systemic, secondary to absorption and metabolism to formalic acid and formic acid. The effects include diminished bladder contractility, incontinence, ureterovesical obstruction, ureteral strictures, acute tubular necrosis, vesicoureteral reflux and toxic myocardiopathy, among other disorders.

After discarding the presence of vesicoureteral reflux with filling cystography (or using Fogarty catheters to avoid reflux) and emptying the bladder of clots, the following recommendations can apply: with the patient under general or epidural anesthesia, the genital area (skin and mucosal membranes) must be protected with baseline, and/or the vagina is to be covered, in order to avoid abrasion secondary to instillation fluid losses. Formalinization should start at low concentrations (1-2%), with increments if needed. The duration of instillation in turn should not exceed 15 min., with an intravesical pressure of less than 15 cmH₂O.

Because of the potential complications of the technique, it should only be used when other more conservative options have failed.

Evidence level: IV.

**Systemic treatments**

4. **Conjugated estrogens**

The mechanism of action whereby conjugated estrogens act in hemorrhagic cystitis has not been fully established. Such treatment is accepted to modulate cellular immune responses and cytokines, and to stimulate endothelial cell activity. The use of conjugated estrogens in hemorrhagic cystitis has been reported to be both effective and ineffective. The relatively low cost of the treatment, its few side effects, ease of administration, and the fact that it does not condition posterior treatment modalities, make it necessary to consider conjugated estrogens among the first-line treatment options.

The administration of estrogens has been associated with hypercoagulability and liver toxicity, as a result, liver enzyme and serum bilirubin determinations are required before starting treatment.

The administration protocol described by Ordemann et al. consists of starting treatment with 6 mg/day fractionated into three doses, followed by gradual increments up to 12 mg/day and/or hematuria control. The resolution of hematuria has been reported to occur from as little as 8 hours post-administration to as long as after 7 days. The treatment is prolonged for 5-16 weeks, with descending conjugated estrogen doses.

Evidence level: IV.

5. **Pentosan polysulfate sodium**

Up to 5% of the pentosan polysulfate sodium administered via the oral route is excreted in urine. Although the precise mechanism of action is not known, this drug repairs the urothelial glycosaminoglycan layer and exerts an antiinflammatory effect. Few studies have been published on the use of pentosan polysulfate sodium, and the patient series have been limited in size, though with long term follow-up that advocates the efficacy of this treatment.

The few side effects, the absence of interactions with other treatments, and the relatively rapid results make it necessary to consider this treatment as a first-time management option.

Evidence level: IV.

6. **Aminocaproic acid**

The use of epsilon aminocaproic acid for the management of hematuria of bladder origin has been described by a number of authors, with different success rates. Its oral administration at a dose of 150 mg/kg/day during 21 days was described by Stefani et al. as an effective way of treating hematuria in 9 patients, with hardly any side effects. Its intravesical application was advocated by Singh et al. as a safe and effective option in 37 patients.

It is necessary to discard possible blood dyscrasias before administering the drug, regardless of the route employed. The short series published to date and the lack of continuity in its use make it necessary to view this treatment option with caution.

Evidence level: IV.
7. **Recombinant factor VIIa**

Recombinant coagulation factor VIIa favors fibrin clot formation at the site of vascular damage, forming a complex with the exposed tissue factor and acting upon the activated platelets. Its use has been authorized in refractory bleeding in patients with inhibitors targeted to factors VIII and IX, in factor VII deficiency, and in Glanzmann thrombasthenia. This treatment has been reported to be effective in patients with thrombocytopenia and platelet disorders, bleeding associated with oral anticoagulation, severe traumatisms and liver diseases, as well as in cases of severe bleeding in adult patients without congenital coagulopathy or inhibitor development.

Few randomized clinical trials have been published on the variety of uses of such therapy, and most publications correspond to clinical notes with small sample sizes. Scarpetini and Rizoli published a review on the use of recombinant factor VIIa (rFVIIa) in the different surgical areas – reporting a decrease in preoperative bleeding in the context of retropubic radical prostatectomy, after administering 20–40 µg/kg of recombinant factor VIIa. However, in the mentioned study, the blood losses in the control group were considerably higher than those considered acceptable for surgery of this type.

The successful use of this treatment after radiotherapy has been reported in the gynecological setting, when all other measures had failed.

Candidates for treatment with rFVIIa must meet the following hematological criteria: hematocrit > 24%; fibrinogen 50–100 mg/dl; platelet count > 50,000 x 10³; and pH > 7.2. In addition, administration must adhere to a series of clinical intervention measures.

The request for recombinant factor VIIa as treatment for radiation-induced cystitis falls within the category of “compassionate drug use.” The recommended dose is 90 µg/kg, and a second dose may be administered after 20 minutes if the desired effect is not achieved. A further number of doses has not been shown to be effective.

Evidence level: IV.

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**Physical measures**

8. **Hyperbaric chamber**

The administration of high-pressure oxygen stimulates angiogenesis in irradiation-damaged tissues. The sessions last 90 minutes on average, administering 100% oxygen in chambers at a pressure of 2–2.5 atmospheres. Treatment consists of one daily session, 5 days a week. The number of sessions varies according to the different literature sources, though a minimum of 15 and a maximum of 60 are recommended before considering other treatment options.

The patients in the reported series received an average of 30 sessions. The start of therapy in the three months following the onset of hematuria implies higher success rates, with a reduction in the number of required sessions. Previous endovesical treatments do not modify the success rates of the hyperbaric chamber. This treatment is well tolerated – the reported complications being auditory and visual barotraumas in isolated cases.

Evidence level: IIb.

9. **Arterial embolization**

Therapeutic embolization for the control of hematuria of bladder origin was described as far back as 1974 by Hald et al., who occluded the internal iliac artery. Interruption of the blood supply yields success rates of about 90% according to the literature. The level of occlusion has been improved from initial embolization of the internal iliac artery to the anterior branch of the internal iliac artery, the superior and inferior vesical arteries, and finally small vessels that perfuse specific regions (i.e., supraselective embolization). Such supraselective embolization has made it possible to reduce the complications of the technique.

The most frequent problem is gluteal pain (gluteal claudication), resulting from embolization of the internal iliac artery and accidentally of the superior gluteal artery. Lower extremity necrosis has also been described, secondary to migration of the occluding material, as well as bladder wall necrosis, and rarely lower limb paraplegia due to embolization of spinal arteries – with the consequent spinal cord effects.

The advantages of the technique are that it can be carried out under local anesthesia, and posterior treatment modalities are not conditioned.

Evidence level: IV.

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**Figure 1 and 2. Supraselective embolization with fibrin plugs.**

10. **Helmstein balloon distension**

In 1966, Helmstein successfully used hydrostatic pressure therapy in bladder tumor treatment, inducing tissue necrosis through compression in 27 of the 35 patients described. He later proposed the same method for the control of hematuria.

Most of the series published in relation to this technique date back to before 1980. It is globally described as useful, simple, with few side effects, but offering only temporary action.

The technique involves fitting a specifically designed balloon (a normal balloon or condom can be used) to the sectioned extremity of a no. 18 Foley catheter. Under epidural anesthesia (in order to eliminate bladder tone), the balloon is inserted through the urethra into the bladder. The balloon is then inflated with saline to a pressure of 10–25 cmH₂O above diastolic pressure. This pressure must be maintained for 6 hours. Although in principle Helmstein recommended the posterior administration of mannitol to deal with meatus edematization following compression, this practice has not been shown to offer advantages in other published series. The hemostatic effect thus obtained persists for 6 months on average.

The most frequently described complication is bladder rupture, detectable by a sudden intravesical pressure change during the procedure. In practically all such situations conservative management is carried out with urethral catheterization.

Evidence level: IV.

11. **Cystectomy**

Surgery is to be considered only when the above described options have failed.

Anatomical dissection may be complicated according to the radiation received and the time elapsed. The type of urinary derivation must be adapted to the individual patient characteristics, the degree of patient...
autonomy, the background disease, and the disease prognosis. Historically, hypogastric artery ligation has been an option when embolization does not prove possible.

**Proposed algorithm**

In the event of hematuria in a patient subjected to pelvic radiotherapy, the presence of bladder neoformations must be discarded, along with hematuria of upper urinary tract origin.

When hematuria is attributed to radiation-induced cystitis, progressive treatment should be provided after hemodynamic stabilization of the patient if needed.

Formalization should be considered only in life-threatening situations where surgery is contraindicated. The following management algorithm is proposed:

**Mild hematuria**

- Urethrocystoscopy
- IVU/CT
- Urine sediment/cytology
- Bladder biopsy
- Start outpatient hyaluronic instillations
- Start process for hyperbaric chamber

**Anemia causing hematuria**

- Urethrocystoscopy in operating room: clot extraction and electrocautery of suspect areas, with biopsy
- Start process for hyperbaric chamber
- Oral treatment:
  - Pentosan polysulfate
  - Conjugated estrogens
  - Aminocaproic acid
  - Bladder instillations: aluminum salts
  - Embolization
  - Helmstein balloon
  - Formalinization
  - Cystectomy

**Conclusions**

A brief account has been provided of the majority of available therapeutic options. There is no single or ideal treatment. Knowing the different options and their administration protocols will allow the urologist to secure a higher success rate in the difficult management of these patients.

**Conflicts of interest**

The authors declare no conflicts of interest.

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