Intravesical Therapies for Radiation Cystitis

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Key Words

Chondroitin sulphate • Cystitis • Glycosaminoglycan layer • Hyaluronic acid • Intravesical therapies • Radiation

Abstract

Objective: The purpose of this study was to summarize developments during the last decade in intravesical treatments for radiation cystitis. Radiation used to treat pelvic malignancies inadvertently damages the urinary bladder leading to acute as well as chronic symptoms. Late sequelae may take years to develop and include storage symptoms and hematuria, which may be life-threatening in severe cases. Conservative measures, surgical interventions, and systematically or intravesically administered agents represent treatment choices. **Methods:** MEDLINE and PubMed were searched to retrieve clinical data on the subject, published in peer-reviewed journals from 2002 onwards. **Results:** Historically referenced intravesical treatments such as aluminium salts and formalin, were not investigated in recent studies. The replenishment of the glycosaminoglycan layer of the bladder mucosa shows promise in reducing acute symptoms and possibly long-term bladder damage, but needs further investigation. Botulinum toxin also represents a new alternative treatment for radiation cystitis but its mechanism of action and efficacy should be evaluated in future trials. **Conclusion:** There is a paucity of data in recent literature regarding the management of radiation cystitis, at least by means of intravesical agents. The replenishment of the glycosaminoglycan layer of the bladder mucosa and the administration of botulinum toxin show promise, but need further investigation.

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Introduction

Radiation is often used in the management of pelvic malignancies, either as primary or as adjuvant treatment. The aim of radiation therapy is to deliver the highest possible doses of radiation to targeted cancer while simultaneously sparing normal surrounding tissues and organs. Nevertheless, in the case of pelvic irradiation, a degree of bladder involvement is inevitable.

Irradiation of the bladder causes pathological changes both during treatment as well as long after its conclusion. In the acute phase, findings concern mainly the bladder mucosa. Histological examination reveals varying degrees of urothelial desquamation, increased vascularity, edema, and infiltration by inflammatory cells [1]. Late radiation effects are found deeper in the bladder wall. Vascular changes such as luminal occlusion, ectasia, necrosis, and hyalinization have been described, accompanied by atrophy and fibrosis of the entire bladder wall resulting in a contracted organ. Radiation appears to cause a combination of histological findings rather than one or a few pathognomonic changes [2].

Pathological changes in the bladder lead to a combination of clinical symptoms known as radiation cystitis. Depending on the time from exposure to radiation, radiation cystitis is classified as acute, occurring within the first 3 months after exposure, or chronic if symptoms develop beyond the acute phase [3]. Chronic radiation cystitis may take years or even decades to manifest. The Radiation Therapy Oncology Group (RTOG) has proposed a classification of radiation cystitis, both acute and chronic, in 5 grades of severity with grade 0 signifying

no symptoms and grade 5 death directly related to radiation toxicity [4]. Chronic cystitis severity also considers the appearance of bladder mucosa on cystoscopy as well as bladder capacity. In lower severity grades storage symptoms such as frequency, nocturia, and urgency predominate but voiding symptoms such as dysuria also occur. Bladder pain, hematuria, and reduced bladder capacity characterize higher severity grades.

The incidence of genitourinary toxicity primarily varies depending on the total radiation dose and radiation delivery techniques as well as time from treatment. For treatment of prostate cancer, for example, incidence of acute grade 0–3 bladder toxicity has been reported to be as high as 53.3% the second week of conventional six-field conformal radiotherapy delivering 78 Gy in 39 fractions [5]. Similar rates of 52.3% have been reported in patients with gynecological malignancy [6]. Acute toxicity in the majority of cases of pelvic irradiation is mild and self limiting. Anticholinergics have been the mainstay of management for storage symptoms despite the paucity of published evidence of their efficacy in the patient population [7]. Analgesics are also of use.

Late toxicity rates are lower but in high severity grades storage symptoms are debilitating and hematuria may become catastrophic. About 7.7% of patients report grade 3 or more genitourinary toxicity at a minimum 7 year follow-up with conventional two-dimensional planning in the historical control RTOG trials of 7,506 and 7,706 of prostate cancer irradiation [8, 9]. With three-dimensional conformal radiotherapy and intensity-modulated radiation therapy late toxicity rates are lower [10]. Management of high grade late radiation cystitis is a particular challenge for the urologist. Various treatments, both systemic and local have been used but generally accepted guidelines are lacking.

The present review aims at summarizing clinical evidence accumulated in the past 10 years on intravesically administered treatments for radiation cystitis in the context of historically referenced therapies. A literature search was performed in MEDLINE and PubMed to retrieve articles in English published in peer review journals from 2002 onwards.

Literature Search Results: Intravesical Treatments for Radiation Cystitis

Glycosaminoglycan (GAG) Replenishment Therapy

The GAG layer was identified in the 1970s as a mucus layer on the surface of the urothelium, acting as a defense

mechanism against urine irritants and noxious solutes, including bacteria. Damage to this layer has been shown in various forms of chronic cystitis including interstitial cystitis and recurrent bacterial cystitis, as well as chemotherapy and radiation-induced cystitis. Therefore intravesical GAG replenishment represents a treatment option for the above mentioned conditions with accumulating evidence of efficacy particularly for interstitial cystitis and recurrent bacterial cystitis [11].

Intravesical GAG replenishment can be achieved by using chondroitin sulphate, hyaluronic acid, a combination of chondroitin sulphate and hyaluronic acid, or heparin. No trials were identified in the literature in the last ten years regarding use of heparin. The combination of hyaluronic acid and chondroitin sulfate showed promising efficacy in initial trials for interstitial cystitis/painful bladder syndrome [12–14], and given the fact that there are 2 commercially available combination formulations, it would represent a possibly useful alternative for radiation cystitis. Unfortunately relevant data are not available.

Chondroitin Sulfate. The use of intravesical chondroitin sulfate 0.2% was reported in 15 patients with radiation cystitis, participating in a multi-nation, prospective, multi-centre, observational trial of GAG replenishment which enrolled 286 patients with various forms of cystitis [15]. The maximum number of instillations was 8 and the recommended schedule of 4–6 weekly instillations followed by further monthly treatments which could be adjusted according to the judgement of the treating physician. At the end of the treatment period of 3 months, daytime micturition frequency decreased from 10.7 ± 0.7 (mean $\pm$ standard error of mean) to 7.4 ± 0.60 and nocturia from 4.7 ± 0.7 to 2.0 ± 0.3 episodes. When severity of urgency and pain were assessed using an 11-point scale (with 0 representing no pain/urgency and 10 pain/urgency as bad as it could be) urgency scores decreased from 7.2 ± 0.5 to 2.3 ± 0.2 and pain intensity from 4.5 ± 0.6 to 1.8 ± 0.3 . All patients and physicians assessed the treatment positively and rated the benefit as “fair”, “good” or “excellent” on a 5-point scale which also included ratings of “good” and “satisfactory”. The average duration of symptoms in the entire study population was 2.8 years but it was not specifically reported for the radiation cystitis group. Intravesical chondroitin sulfate administration was generally well tolerated.

A comparative pilot study in 20 patients planned for primary or adjuvant radiotherapy for endometrial or cervical cancer examined the feasibility and efficacy of intravesical instillations with 40 ml chondroitin sulfate

0.2% solution in preventing or reducing acute radiation cystitis [16]. Ten patients consented to weekly vesical instillations for the duration of radiation therapy while the remaining 10 did not opt for intravesical treatment and served as controls. The Urogenital Distress Inventory was used to measure quality of life related to micturition. It includes symptom domains concerning overactive bladder symptoms, incontinence, obstructed micturition, and pain, with scores ranging from 0 to 100 and lower scores indicating less bother. The acceptability/bother of intravesical instillations was assessed by four questions with answers ranging from 0 (the highest possible acceptability) to 10 (the lowest possible acceptability) on a Visual Analogue Scale (VAS). Five more questions with 10 point VAS scores were used to assess bladder pain. At the end of treatment, median Urogenital Distress Inventory domain scores at or above the median baseline scores were recorded in controls and at or below median baseline scores in the instillation group for overactive bladder, incontinence, and obstructive voiding. Bladder pain VAS scores peaked during treatment in the control group (median 1, range 0–5) but only after treatment in the chondroitin group (median 1, range 1–3). One patient, treated with radiotherapy and hyperthermia, discontinued the instillations after week 4 due to urethral pain. The acceptability VAS score had a median value of 1 (range 0–3) after the last instillation.

The authors concluded that there was a clear trend towards less bothersome micturition symptoms in women who had bladder instillations with chondroitin sulfate 0.2% solution during pelvic radiotherapy and instillations were generally well tolerated. Limitations of this study included the small number of patients, the diversity of concomitant interventions, and most importantly, the lack of randomization, resulting in younger patients who were more eager to prevent radiation cystitis and less likely to have voiding symptoms consenting to instillation.

Hyaluronic Acid. In a single-centre, retrospective study of patients diagnosed with cervical or endometrial cancer and treated with brachytherapy with (48 patients) or without (47 patients) intravesical instillations of hyaluronic acid [17, 18], rates of acute and late vesical toxicity were recorded using the RTOG criteria. In all the brachytherapy sessions the percentage of patients presenting acute vesical toxicity was lower in the hyaluronic acid group, the differences being statistically significant after the 2nd (20.8% vs. 40.4%) and 4th sessions (10.9% vs. 31.9%). No patients in the hyaluronic acid group presented vesical toxicity after six months of follow-up.

Over the 5 year study period, the percentage of patients presenting vesical toxicity of degree 2 or more was significantly lower in the intravesical instillation group (2.08% vs. 12.8%; $p < 0.05$).

The efficacy of intravesical administration of hyaluronic acid in treating symptoms of radiation-induced hemorrhagic cystitis was compared to that of hyperbaric oxygen in a prospective, randomized study [19]. In total 36 patients with cervical, rectal, or prostate cancer were included, in which 16 had macroscopic hematuria without clot formation and the remaining 20 had hematuria with clots or requiring transfusion. In the hyaluronic acid group 16 patients received four 40 mg weekly instillations followed by two monthly ones. In the hyperbaric oxygen group, 20 patients received 30 treatments of 100% oxygen in a hyperbaric chamber at a pressure of 2.5 atm for a minimum time of 60 min. Efficacy was assessed every 6 months for a period of 18 months. Symptoms of hematuria, frequency of voiding, and the VAS of pelvic pain (range 0–10) were evaluated before and after treatment. Overall response rates were comparable between groups. Significant improvements in urinary frequency were achieved with both treatments at the 6 month follow-up, only with hyaluronic acid instillations at 12 months, and with neither treatment at 18 months. Both treatments were associated with significant improvements in bladder pain (VAS) for the entire follow-up period. Both treatments were well tolerated but a higher incidence of urinary tract infections was observed in the hyaluronic acid group (42.8% vs. 10% in the hyperbaric oxygen arm) limited to the first 6 months of the study. One patient in the hyaluronic acid arm required a second course of intravesical instillation to treat recurrence of hematuria at 15 months follow-up. The authors concluded that intravesical instillation of hyaluronic acid represents an alternative therapy in the management of radiation-induced hemorrhagic cystitis. They acknowledged the small number of patients and short follow-up as limitations of their study.

Historical Intravesical Instillations

Aluminum. Aluminum salt irrigation for the treatment of severe hematuria was first described 30 years ago [20] in 6 patients with radiation cystitis, bladder carcinoma, and hemorrhagic cystitis. Treatment with a 1% solution was effective and well tolerated. In the following years a few reports of satisfactory efficacy were published [21–23], but they were soon outnumbered by reports of severe aluminum toxicity, primarily central nervous toxicity [24, 25]. Renal insufficiency and a large absorptive bladder area are known risk factors for aluminum toxicity.

Alum irrigation is frequently mentioned as a treatment option for severe hemorrhage related to radiation cystitis in textbooks and review papers but no data on its use have been published in PubMed indexed journals for at least 2 decades, apart from a few case reports [26].

Formalin. The use of intravesical instillation of formalin for the cessation of bleeding related to radiation cystitis dates from the 1970s [27], even though the method was first described for the management of bladder cancer [28]. In a retrospective analysis of 25 cases of severe bladder hematuria, 15 relating to radiation, good results were reported in 88% of cases, who achieved hemostasis during a mean of 4 months [29]. Formalin achieves hemostasis by precipitation of cellular proteins in the bladder mucosa producing an occlusive and fixative action on telangiectatic vessels. This mechanism is also responsible for formalin's devastating complications. Its diffusion into the sub-urothelial tissues leads to chemical cystitis, fixation of the bladder musculature, and a small contracted bladder. Formalin can also cause fixation of the intramural ureter and, in cases of reflux in the upper urinary tract, tubular necrosis and anuria. Therefore intravesical formalin use should only be considered when the bladder has been isolated by a urinary diversion.

In 1997 the endoscopic placement of 5% formalin soaked cotton pledgets onto bleeding areas was described in a patient with hemorrhage due to radiation cystitis, refractory to intravesical saline, alum, prostaglandin E1, and estrogen [30]. The technique, aimed at avoiding the fixative effects of formalin on non-bleeding bladder areas, was successful with no subsequent bleeding for at least 16 months of follow-up. Since then only a case report of this technique has been published [31].

Other Intravesical Agents

The intravesical use of ozone [32] and recombinant factor VIIa [33] were described in case-reports for the treatment of hematuria due to radiation cystitis.

Intravesical Interventions

Botulinum Toxin. Endoscopic bladder injection with botulinum toxin which, as was originally known, blocks acetylcholine release at neuromuscular junctions, is an increasingly recognized treatment for detrusor over-activity [34]. Recent research showed that it also blocks release of neurotransmitters, inhibits vanilloid and P2X receptors, cyclooxygenase-2 expression, and suppresses inflammatory reactions, thus providing the rationale for botulinum toxin use in the treatment of storage symptoms of various pathophysiologies [35].

Data on six patients with radiation cystitis, refractory to conventional therapy, who were treated with botulinum toxin in a small retrospective review series, were published in 2008 [35]. Four men with radiation cystitis following prostate cancer irradiation and two women with radiation cystitis following external beam radiation for cervical cancer were given sub-mucosal bladder injections of 200 units of botulinum toxin A. One patient did not improve, 3 were moderately improved, and 2 significantly improved. The mean bladder capacity increased from 125 to 250 ml and urinary frequency decreased from 14 to 11 episodes per day, at 2 months after injection. There was no significant change in post void residual and no cases of retention. The authors concluded that results of this first use of botulinum toxin in the treatment of radiation cystitis were promising but needed to be further investigated.

Use of Lasers for Hemostasis. Electrocautery has been used for hemostasis in cases of radiation cystitis-related hematuria. Recently hemostasis using other sources of energy was investigated. The Nd:YAG laser was used to successfully treat 42 patients [36] with no recurrence at a mean follow-up period of 14 months. The argon laser achieved hemostasis in all 7 patients with severe radiation induced hematuria [37]. Patients were discharged the following day with clear urine and there was only one treatment failure which required re-treatment at a mean follow-up of 15 months. The 980-nm diode laser achieved a mean hematuria-free time of 11 months in four patients with severe hemorrhage due to chronic radiation cystitis refractory to conservative treatment and standard electrocautery [38]. The green light achieved hemostasis in 10 patients with intractable hematuria with only one requiring re-treatment at 7 months because of recurrence of significant bleeding [39].

Discussion

Even though radiation cystitis can develop during or soon after pelvic irradiation the term is routinely used in everyday practice to describe late effects. The reason is that the acute effects are often mild and self-limiting, requiring little or no intervention. On the contrary, hematuria, a late effect of bladder irradiation, is the symptom that most commonly requires the urologist's intervention and can be life threatening. Management is difficult, and safe and effective interventions are lacking as well as treatment guidelines.

The challenge that management of hematuria represents, explains the fact that the majority of published data reviewed refer to treatment options for this end-stage symptom. Historically referenced intravesical treatments for cessation of bleeding related to radiation cystitis, such as aluminum salts, formalin, silver, and many others are difficult to apply without significant adverse affects. As a result no data on their use have been published for many years. Nevertheless they are considered effective when life-threatening hematuria fails to respond to first-line measures (bladder irrigation and/or cystoscopy with fulguration of bleeding points). Surgical intervention is considered a last-resort measure with high morbidity.

As far as management of storage symptoms is concerned, botulinum toxin may represent an alternative treatment worth investigating but the only significant changes in conservative management of radiation cystitis in recent years are hyperbaric oxygen therapy and intravesical instillation of agents that replenish the GAG layer. The later is relevant to the present review.

The rationale behind GAG replenishment is the evidence of radiation induced GAG layer damage as well as the efficacy of GAG replenishment in other conditions with chronic storage symptoms, interstitial cystitis in particular. Indeed the few initial studies summarized in this review show promise in preventing or ameliorating

at least acute symptoms related to bladder irradiation. In fact efficacy is suggested to be comparable to that of hyperbaric oxygen. Evidence also suggests that chronic sequelae may also be reduced but clearly larger, adequately designed, and powered trials are needed to investigate this [40].

The rarity of chronic radiation cystitis, especially with newer, advanced radiation delivery methods (such as intensity-modulated radiation therapy and image-guided radiation therapy), and the more frequent use of cystectomy for bladder cancer management, makes obvious the difficulties in identifying enough patients to participate in well designed randomized studies. Nevertheless, every effort in this direction should be made.

Conclusion

The literature on intravesical treatments of radiation cystitis is sparse. The replenishment of the glycosaminoglycan layer of the bladder mucosa, with chondroitin and/or hyaluronic acid represents the most promising area for future research in the management of acute symptoms and prevention of late sequelae. No developments have been identified in intravesical treatments targeting radiation cystitis-related hematuria.

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