Prophylactic vesical instillations with 0.2% chondroitin sulfate may reduce symptoms of acute radiation cystitis in patients undergoing radiotherapy for gynecological malignancies

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ORIGINAL ARTICLE

Prophylactic vesical instillations with 0.2% chondroitin sulfate may reduce symptoms of acute radiation cystitis in patients undergoing radiotherapy for gynecological malignancies

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Abstract
Introduction and hypothesis We studied the feasibility and efficacy of intravesical instillations with 40 ml chondroitin sulfate 0.2% solution to prevent or reduce acute radiation cystitis in women undergoing pelvic radiotherapy.
Methods In a comparative pilot study in 20 patients, half of the patients received instillations. Instillations' bother was measured with visual analog scores (VAS, 0–10); bladder pain, with VAS; micturition-related quality of life, with the urogenital distress inventory (UDI).
Results One of the instilled patients discontinued the instillations. The first median "acceptability"-VAS was 0 (range, 0–3); the last median was 1 (range, 0–3). "Bladder pain"-VAS peaked halfway in the treatment among controls (median, 1; range, 0–5) and after treatment in the instilled patients (median, 1; range, 1–3). UDI scores showed over time median follow-up scores *at or above* median baseline scores in controls and *at or below median* baseline scores in instilled patients.
Conclusion Intravesical instillations with chondroitin sulfate 0.2% solution may decrease the bother related to bladder symptoms and are well tolerated.

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Keywords Acute radiation cystitis · 0.2% Chondroitin sulfate · Intravesical instillations · Overactive bladder · Pelvic radiotherapy

Abbreviations

RC	Radiation cystitis
GAG layer	Glucosamino-glycane layer
UDI	Urogenital distress inventory
VAS	Visual analog scale
$T=0$	Time point before radiotherapy
$T=4$	Time point in the fourth week of radiotherapy
$T=8$	Time point after radiotherapy
RCT	Randomized clinical trial

Introduction

Acute radiation cystitis (RC) is a common and debilitating problem in patients undergoing radiotherapy for gynecological malignancies [1]. Acute RC symptoms develop on average at 2 to 3 weeks after the start of treatment in up to 24–30% of patients, and these symptoms include painful micturition, urgency, frequency, and nocturia [1, 2]. These overactive bladder symptoms are known to seriously impair quality of life [3]. Although this acute condition is claimed to be self-limiting, it may result in chronic RC, which carries the risk of life-threatening morbidity [4–6]. Treatment of acute RC is only symptomatic, and up to now, no preventive measures have been studied.

The pathophysiology of acute RC is not exactly clear, but the bladder wall is internally built up by fast-dividing uroepithelium, susceptible to radiation damage. The uroepithelium is coated by the glucosamino-glycane (GAG)

layer, preventing urinary irritants to reach the underlying sensory nerves. When the uroepithelium is damaged, this results in insufficiency of the GAG layer, and consequently, silent C-fibers are depolarized by urinary irritants, leading to RC symptoms [5, 7]. Acute RC usually occurs 3 to 6 weeks after starting radiation therapy [5]. Up to 3 months after the start of radiation therapy, the occurrence of RC is often called the acute form [4, 8].

Endometrial and cervical malignancies can be treated with primary or adjuvant pelvic radiotherapy. The mode of treatment depends on disease-related characteristics, such as size and extension of the tumor and, to a lesser extent, on patient characteristics [8, 9]. The severity of morbidity during and after treatment depends on the radiotherapy dosage and volume [9, 10]. Since the radiation schedule is determined by disease-related characteristics, the prevention of acute RC can therefore not easily be accomplished by lowering the dose and volume but should be sought for direct protection of the bladder.

Based on animal studies demonstrating that intravesical instillation with chondroitin sulfate solution is capable of coating a damaged bladder wall, we hypothesize that prophylactic instillations on patients undergoing radiotherapy for gynecologic malignancies may limit the risk of distressing RC symptoms [11]. Our hypothesis is supported by the observation that in interstitial cystitis (IC) patients, GAG layer replenishment therapy has been proven to be effective [12, 13]. By keeping the coating of the urothelium intact during the radiotherapy treatment, the cells could be less damaged by urinary irritants. Short-term protection of the GAG layer and thus limitation of the risk on acute RC might even reduce the risk on chronic RC which has even more decrementing effects, although this possible long-term effect is outside the scope of this pilot study.

Instillation with chondroitin sulfate has no known adverse effects but is time-consuming and possibly burdensome, and most patients will need the assistance of a healthcare professional to undergo instillations.

The aims of this pilot study were to investigate the feasibility and efficacy of intravesical instillations with chondroitin sulfate 0.2% solution to prevent or reduce acute RC in patients treated with pelvic radiotherapy for gynecological cancer.

Patients and methods

We performed a comparative pilot study to evaluate the feasibility and efficacy of chondroitin sulfate 0.2% solution to prevent or reduce RC in endometrial or cervical cancer patients who did and did not receive instillations. The study was performed between September 2007 and September 2009 in the Academic Medical Center Amsterdam, The Netherlands.

We included patients who met the following criteria: aged 18 years or older, planned for primary or adjuvant radiotherapy for endometrial or cervical cancer and able to complete a Dutch questionnaire. We excluded patients who were planned to only undergo brachytherapy, patients with previous surgery of the lower urinary tract or patients with a (suprapubic) catheter in situ.

We used 40-ml 0.2% solution of chondroitin sulfate (Gepan® instill) for the intravesical instillations (Pohl-Boskamp, Hohenlockstedt, Germany). In accordance with comparative studies in IC patients, we planned weekly instillations during the 6 weeks that radiotherapy lasted [13]. The study coordinator (MH) did the instillations at the radiotherapy outpatient clinic after a course of radiotherapy, as patients had to have a full bladder before undergoing radiotherapy and were allowed to empty the bladder afterwards. These instillations were planned 2 days after chemotherapy, if applicable, as the hyperhydration during and the day after chemotherapy might have an influence on the effect of the intravesical instillation. A single-use catheter with an outer-side diameter of 4 mm (12 Ch) was used to first empty the bladder and then fill the bladder with the 40 ml solution. Patients were asked not to void at least 2 h after the instillation.

We included 20 uterine or cervical cancer patients consecutively at the outpatient department before start of treatment. Ten patients consented to have weekly intravesical instillations and ten consented to participate as control patients. The control group only completed the set of questionnaires. Choice of treatment was left at the discretion of the patient until the planned total of ten patients per group was reached.

During 8 weeks, i.e. before, during and after radiotherapy, patients weekly completed the questionnaires: four questions to quantify the acceptability of the intervention using visual analog scale (VAS) scores ranging from 0 to 10, with lower scores indicating higher acceptability. These questions were about distress: from coming to the outpatient clinic to receive the instillation, from the insertion of the single-use catheter for the instillation, from holding the instilled fluid in the bladder after instillation and from the instillation in total. Five questions using VAS scores were asked to measure bladder pain related to voiding: bladder pain at the moment when urge starts, just before voiding, during voiding, just after emptying the bladder, when not having the urge to void or just after voiding. The urogenital distress inventory (UDI) measured quality of life related to micturition. The UDI has five symptom domains, with scores ranging from 0 to 100, with a higher score corresponding with more bother of that symptom [14]. Descriptive statistics are reported.

Adverse effects of chondroitin sulfate are not clearly known. The substance is not absorbed into the body. In one

study, a mild rash has been mentioned, but furthermore, no serious complications related to chondroitin sulfate administered intravesically have been described [12]. Because of the risk of developing urinary tract infection (UTI) when regularly catheterizing, we checked with a urine culture when the radiotherapist had clinical suspicion of UTI.

This study was approved by the local medical ethical committee. The participants signed an informed consent.

Results

Ten patients had intravesical instillations. One patient, treated with radiotherapy and hyperthermia, discontinued the instillations after week 4 due to urethral pain, and she refused to complete the subsequent questionnaires.

The median age of the instillation group was 55 years (range, 32–75), and that of the controls was 64 years (range, 47–93). For more patient characteristics, see Table 1.

The "acceptability of instillations"-VAS had a median score of 0 (range, 0–3) after the first instillation and a median of 1 (range, 0–3) at week 6 (last instillation). "Bladder pain"-VAS levels peaked at week 4 among the controls (median, 1; range, 0–5) and at week 8 in the instillation group (median, 1; range, 1–3) (data not shown).

Table 2 shows the symptom scores of both groups before (T=0), halfway (T=4) and after (T=8) radiotherapy.

Table 1 Characteristics of study groups (numbers of patients, unless indicated otherwise)

Intervention group, N=10			Control group, N=10	
Age (median, range)		55 (32–75)		64 (47–93)
Uterine cancer	*Endometrial*	*4*		*7*
	Carcinosarcoma	*1*		
FIGO stage			IC G2	1
	IIA G2	1	IC G3	1
	IIIA	1	IIA G3	1
	IIIC G2	1	IIB G2	1
	Recurrence[a]	1	IIIA G1	1
	Carcinosarcoma IC	1	IVB	1
			Unknown[a]	1
Surgery	AUE+BSO	3	AUE+BSO	4
	AUE±LND	1	AUE±LND	2
	AUE+BSO+LND	1		
Postoperative RT (Grays)	(46)	4	(46)	4
	(48.6)	1	(48.6)	2
Primary RT (Grays)			(40.05)	1
Brachytherapy (Grays)	(10)	3	(10)	5
			(12)	1
Chemotherapy				2
Cervical cancer		*5*		*3*
FIGO stage	IBI	1	IBI	2
	IB2	1	IIIB	1
	IIB	2		
	IIIB	1		
Surgery	LNDebulking	3	RH+LND	1
			VH	1
Postoperative RT (Grays)	(46)	3	(46)	2
Primary RT (Grays)	(46)	2	(46)	1
Brachytherapy (Grays)	(24)	5	(10)	1
			(24)	1
			(28)	1
Hyperthermia	1 h/week	1		1
Surdosage parametria/LN		4		2
Chemotherapy		4		1

G grade of tumor cell differentiation, *AUE* abdominal hysterectomy, *BSO* bilateral salpingo-oophorectomy, *LND* lymph node dissection, *RT* radiotherapy, *LNDebulking* lymph node debulking, *RH+LND* radical hysterectomy and lymph node dissection, *VH* vaginal hysterectomy–cervical cancer was coincidentally found, *FIGO* international federation of gynaecologic oncology, *LN* lymph nodes

[a] Recurrence–previous treatment did not include radiotherapy, only AUE and BSO

Table 2 Urogenital distress inventory (UDI) domain scores

	T=0		*T*=4		*T*=8	
	Median (range)		Median (range)		Median (range)	
	Instillation (*n*=10)	Control (*n*=7)	Instillation (*n*=9)	Control (*n*=6)	Instillation (*n*=7)	Control (*n*=7)
OAB	22 (0–66)	11 (0–55)	11 (0–33)	38 (0–55)	22 (0–66)	33 (0–55)
INC	25 (0–50)	17 (0–33)	0 (0–50)	17 (0–83)	0 (0–50)	33 (0–83)
OBS	0 (0)	0 (0–66)	0 (0–33)	25 (0–66)	0 (0–17)	17 (0–33)
PAIN	0 (0–50)	0 (0–33)	0 (0–33)	8 (0–17)	0 (0–33)	0 (0–17)

The range of each domain score was 0–100; a higher score indicating more distress

T=0 measurement before the start of radiation, *T=4* measurement in the fourth week of radiation, *T=8* measurement in the eighth week after the start of radiation and radiotherapy had ended, *OAB* overactive bladder, *INC* incontinence, *OBS* obstructive voiding, *PAIN* painful bladder/pelvic area

Diverging patterns over time were noted with median follow-up scores *at or above* median baseline scores in controls and *at or below median* baseline scores in the instillation group for overactive bladder, incontinence and obstructive voiding, respectively.

During the radiotherapy treatment period, urine was cultured for five patients of the instillation group and four of the control group. None of the instillation patients and one patient of the control group had a UTI.

Discussion

We observed a clear trend towards less bothersome overactive bladder–urinary incontinence–and obstructive micturition symptoms in women who had bladder instillations with chondroitin sulfate 0.2% solution during pelvic radiotherapy treatment for cervical or endometrial cancer. Added to our observation that these instillations are well tolerated, the group of patients receiving instillations reported less distress from overactive bladder symptoms during the period of radiotherapy compared to controls.

Some limitations of this pilot study need to be discussed. First, the number of included patients is limited. Before the start of this study, the tolerability and the efficacy of the instillations for this indication were unknown. We performed the study to generate a hypothesis about this possibly new preventive measure, and therefore, the limited number of included patients was appropriate. Moreover, even though the sample size was small, less distress from urogenital symptoms was reported by patients that had the experimental treatment.

The absence of randomization could also be seen as a limitation of our study. Our primary aim, however, was to evaluate the feasibility of an intervention in patients who undergo a demanding treatment at the same time. As questions arose about the willingness to undergo instillations within the research group, we came to the agreement to give patients a choice to receive the instillations accepting the selection bias.

The heterogeneous treatment modalities are the final limitations we would like to address. Different types of hysterectomy are known to be associated with different bladder or voiding dysfunctions [15, 16]. The uterine cancer patients in the instillation and control groups were comparable in surgical treatments. The difference between cervical cancer patients in the two study groups was that radical hysterectomy and vaginal hysterectomy were performed in the control group, and only lymph node debulking without radical hysterectomy was performed in the instillation group. We do not expect more bladder symptoms in the control group because of the hysterectomies, as the instillation group undergoing lymph node debulking had larger tumors, which might cause overactive bladder symptoms as well. Furthermore, we excluded patients who used a catheter to void to have some indication of a good bladder function before radiotherapy.

The strength of our study is that, even though these patients undergo very intense treatment, they mostly completed the intensive study protocol receiving the instillations and completing the questionnaires. This might be explained by the patients' eagerness to prevent any possible side effect and by the tolerability of instillations. The control group in this study only completed the questionnaires, without a direct gain from the study, but were very compliant in completing the questionnaires.

Another strength of our study is that we used validated pelvic floor-related quality of life questionnaires to measure the urogenital symptoms, measuring for the first time these symptoms in patients currently treated for gynecological malignancies.

A final remark that could be made about this study is that the intervention group is younger than the controls and therefore might have less urogenital symptoms. An explanation for the age difference could be that younger

patients are more willing to reduce treatment-related side effects than older patients with instillations. Above that, the intervention group started with higher symptom scores than the controls, which pleads against younger age being associated with less bother of symptoms. Obviously, a randomized clinical trial (RCT) should be performed to evaluate whether age is a risk factor for more symptoms. We felt, from an ethical point of view, that the feasibility of the instillations had to be examined in these patients prior to an RCT. The refusal to continue the instillations of only one patient due to urethral pain after the fourth instillation makes the instillations seem a feasible intervention.

As the urogenital symptoms were less bothersome in the intervention group than in the control group, we will try to explain this. The current policy for patients with acute RC symptoms is usually conservatively with analgesics and anticholinergics [6]. Therefore, we cannot compare our results with those of previous studies. Chondroitin sulfate 0.2% solution has been studied before in the chronic cystitis condition, including RC [13]. The pathophysiology of chronic and acute RC is different, which makes the results also difficult to compare to ours. The probable working mechanism of the intravesical instillations with chondroitin sulfate 0.2% solution to prevent or reduce acute RC is that the impermeability of the urothelium for urinary irritants is sustained by coating it with the chondroitin sulfate [11]. By protecting the urothelium from these irritants, the acute bothersome symptoms do not occur or when they occur, do so to a lesser extent. The largest difference between the instillation and control groups in bother of overactive bladder symptoms, expressed by the UDI domain score OAB, was found in the fourth week of treatment. At that time, patients had received 4 weeks of radiotherapy. Acute symptoms occur 3 to 6 weeks after the start of radiotherapy [5]. It could be that the instillation group had the most beneficial effect during the 6 weeks of instillation and that, after the end of the radiation treatment and the six instillations, this effect decreased.

Conclusion

The results of this pilot study show that intravesical instillations with chondroitin sulfate 0.2% solution are well tolerated by patients undergoing pelvic radiotherapy for a gynecological malignancy. Additionally, the instillations appear to reduce overactive bladder symptoms during the period of radiotherapy. Whether the restricted severity of symptoms following radiotherapy can be entirely explained by the effectiveness of chondroitin sulfate itself or by other factors such as additional attention that was given to the intervention group, this needs to be assessed by a double-blind placebo-controlled RCT. If confirmed, the evaluated intervention could be the first described preventive measurement for the occurrence of acute RC. If the observation would hold true in future studies, this could implicate a major improvement of quality of life in women undergoing radiotherapy.

Conflicts of interest Pohl-Boskamp provided an unrestricted research grant of this physician-initiated study.

References

1. Shakespeare TP, Lim KH, Lee KM, Back MF, Mukherjee R, Lu JD (2006) Phase II study of the American Brachytherapy Society guidelines for the use of high-dose rate brachytherapy in the treatment of cervical carcinoma: is 45–50.4 Gy radiochemotherapy plus 31.8 Gy in six fractions high-dose rate brachytherapy tolerable? Int J Gynecol Cancer 16(1):277–282
2. Yalman D, Arican A, Ozsaran Z, Celik OK, Yurut V, Esassolak M et al (2002) Evaluation of morbidity after external radiotherapy and intracavitary brachytherapy in 771 patients with carcinoma of the uterine cervix or endometrium. Eur J Gynaecol Oncol 23 (1):58–62
3. Coyne KS, Sexton CC, Irwin DE, Kopp ZS, Kelleher CJ, Milsom I (2008) The impact of overactive bladder, incontinence and other lower urinary tract symptoms on quality of life, work productivity, sexuality and emotional well-being in men and women: results from the EPIC study. BJU Int 101(11):1388–1395
4. Maduro JH, Pras E, Willemse PH, de Vries EG (2003) Acute and long-term toxicity following radiotherapy alone or in combination with chemotherapy for locally advanced cervical cancer. Cancer Treat Rev 29(6):471–488
5. Butrick CW (2000) Radiation cystitis. In: Howard FM, Perry CP, Carter JE, El-Minawi AM (eds) Pelvic pain: diagnosis and management, 1st edn. Williams and Wilkins, Baltimore
6. Pavlidakey PG, MacLennan GT (2009) Radiation cystitis. J Urol 182(3):1172–1173
7. Butrick CW, Sanford D, Hou Q, Mahnken JD (2009) Chronic pelvic pain syndromes: clinical, urodynamic, and urothelial observations. Int Urogynecol J Pelvic Floor Dysfunct 20 (9):1047–1053
8. Farquharson DI, Shingleton HM, Sanford SP, Soong SJ, Varner RE Jr, Hester S (1987) The short-term effect of pelvic irradiation for gynecologic malignancies on bladder function. Obstet Gynecol 70(1):81–84
9. Jereczek-Fossa BA, Badzio A, Jassem J (2003) Factors determining acute normal tissue reactions during postoperative radiotherapy in endometrial cancer: analysis of 317 consecutive cases. Radiother Oncol 68(1):33–39
10. Perez CA, Grigsby PW, Lockett MA, Chao KS, Williamson J (1999) Radiation therapy morbidity in carcinoma of the uterine cervix: dosimetric and clinical correlation. Int J Radiat Oncol Biol Phys 44(4):855–866

11. Kyker KD, Coffman J, Hurst RE (2005) Exogenous glycosaminoglycans coat damaged bladder surfaces in experimentally damaged mouse bladder. BMC Urol 5:4
12. Nordling J, van Ophoven A (2008) Intravesical glycosaminoglycan replenishment with chondroitin sulphate in chronic forms of cystitis. A multi-national, multi-centre, prospective observational clinical trial. Arzneimittelforschung 58(7):328–335
13. Steinhoff G, Ittah B, Rowan S (2002) The efficacy of chondroitin sulfate 0.2% in treating interstitial cystitis. Can J Urol 9(1):1454–1458
14. van der Vaart CH, de Leeuw JR, Roovers JP, Heintz AP (2003) Measuring health-related quality of life in women with urogenital dysfunction: the urogenital distress inventory and incontinence impact questionnaire revisited. Neurourol Urodyn 22(2):97–104
15. Roovers JP, van der Bom JG, Huub van der Vaart C, Fousert DM, Heintz AP (2001) Does mode of hysterectomy influence micturition and defecation? Acta Obstet Gynecol Scand 80(10):945–951
16. Jackson KS, Naik R (2006) Pelvic floor dysfunction and radical hysterectomy. Int J Gynecol Cancer 16(1):354–363