

TREATMENT WITH INSTILLATION OF HYALURONIC ACID IN PATIENTS WITH A HISTORY OF PELVIC RADIATION THERAPY AND URINARY STORAGE SYMPTOMS

Hypothesis / aims of study

Pelvic radiotherapy for the treatment of tumours located in the pelvis is not free of the risk of secondary irradiation of the bladder, producing a certain histological changes and it can result in both acute and chronic bladder injuries. Of these, the most evident and studied is radiation-induced hemorrhagic cystitis, although other urinary symptoms like frequency, urgency, incontinence, dysuria or pelvic pain has been described.

Therefore, the objective of our paper is to evaluate the clinical utility of bladder instillation of hyaluronic acid in patients with a history of pelvic radiation therapy and storage symptoms with failure of previous treatment with anticholinergic

Study design, materials and methods

We considered 39 consecutive patients with storage urinary symptoms (defined as urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence) due to post radiation cystitis treated with bladder instillation of hyaluronic acid. Severe urgency episodes with or without incontinence was measured using the PPIUS (Patient Perception of Intensity of Urgency Scale). Eligible patients had \geq three severe urgency episodes with or without incontinence during the 3-day voiding diary period, defined as PPIUS grades 3 and 4, and \geq eight micturitions/24 hours (1). Prior to instillation, all patients received but did not benefit (persistence of urgency) from antimuscarinic/mirabegron (at least 8 weeks)

Pre and post-treatment lower urinary tract symptoms, continence and quality of life were assessed by validated questionnaires. All patients completed the IPSS/QI, ICIQ-UI SF and BPIC questionnaires: at baseline (**baseline**), after the ten instillations (**treatment period**) and during the follow-up (**follow-up period**). Written informed consent was obtained from all.

Pre-treatment assessment with flexible cystoscopy were performed in all cases. In many cases, urodynamic study (MMS Solar ®, city) was performed according ICS criteria.

In accordance with comparative studies in interstitial cystitis patients, we planned weekly instillations during the 6 weeks and biweekly for two months. Then, in improved patients, we extend the treatment monthly for at least 4 months.

The **efficacy of the treatment** was evaluated after the ten instillations and the **maintenance of result** during the last follow-up each patient visit. **Successful treatment** was considered in patients with $<$ three severe urgency episodes with or without incontinence during the 3-day voiding diary period, defined as PPIUS grades 3 and 4, and $<$ eight micturitions/24 hours(1). Post-treatment complications were evaluated according to Clavien Classification of Surgical Complications

Statistical analysis (SPSS-19.0®) of quantitative variables was performed by means of the two-tailed Student t test. Chi-square was applied to qualitative variables. Logistic univariate and multivariate regression model was employed to assess the potential predictors of successful treatment outcomes. Statistical significance was defined as $p < 0.05$. Sample size was calculated in 30 patients (confidence level 95%).

Results

From April 2005 and January 2016, 39 patients were treated, 28 males and 11 females. The median age was 69 years (range 36-85). Initial radiotherapy treatment was: salvage external beam radiotherapy after radical prostatectomy (13 patients), cervix brachytherapy (9 patients), prostate cancer external beam radiation (7 patients) prostate cancer brachytherapy (6 patients), adjuvant radiotherapy of rectal carcinoma(3 patients) and adjuvant radiotherapy for ovarian cancer (1 patient). The median period of time from the initial pelvic radiotherapy and the intravesical instillations was 30 months (range: 6-407). **The median follow-up was 23 months (5-129).**

A cystoscopy was performed in all patients before starting treatment to assess the percentage of presence of **abnormal bladder findings**. Only in seven patients (20%) we don't observe lesions. Urodynamic study was conducted in 24 of 39 patients. Cystometry was pathological in all cases: detrusor overactivity (17 patients), increased bladder sensation (3 patients) and low bladder compliance (4 patients). In any patient cystometry was normal. However, during Pressure Flow Studies we just diagnosed three patients with bladder outlet obstruction

The IPSS score descended statistically significant after the treatment ($p=0.007$). In addition, the results obtained are kept during the period of maintenance ($p=0.810$). The question relating to the urgency voiding (Item 4), also presented a significantly descent ($p=0.012$)

The ICIQ-UI SF score descended statistically significant after the treatment ($p=0.003$). In addition, the results obtained are kept during the period of maintenance ($p=0.346$).

After the first ten instillations, 21 patients (53.8%) presented $<$ three severe urgency episodes during the 3-day and $<$ eight micturitions/24 hours (**successful treatment**). During follow-up, 18 of 21 patients (85.7%) maintained reduction of in the number of severe urgency episodes and micturitions. In univariate analysis, the success rate in women (81.8%) was superior to the men (42.9%) ($p=0.039$). The absence of lesions in the bladder neck also was a positive factor in univariate analysis. However, in the multivariate analysis, the only factor related was the gender.

Interpretation of results

Although most studies focus on severe hemorrhagic cystitis (grades III-IV), other urinary symptoms like frequency, urgency, incontinence, dysuria or pelvic pain has been described. It has been hypothesized that post-radiation lower urinary tract symptoms could be pathophysiologically related to a disruption of the layer of the bladder mucosa with consequent loss of glycosaminoglycans (GAGs).

The first choice in the treatment of the bladder storage symptoms must be anticholinergic treatment, although there are no publications relating to this type of patients(2). If they do not work, the second line of treatment should be GAG replenishment therapy by instillation of hyaluronic acid or chondroitin sulfate and this treatment has been suggested as a viable treatment option to treat post-radiation lower urinary tract symptoms (3).

Concluding message

There is a scarcity of data in the literature regarding the mode of action of hyaluronic acid as well as its effectiveness, however this article demonstrates its clinical utility in with chronic storage symptoms after pelvic radiotherapy, with a few secondary effects and the maintenance of positive effects during follow-up. Our results suggests that hyaluronic acid may be considered for further studies, including randomized controlled trials with adequate power.

References

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Disclosures

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