Title page

The effect of intravesical instillations with Hyaluronic Acid on sexual dysfunction in women with recurrent urinary tract infections (RUTI).

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Condensation

Recurrent urinary tract infections are associated with sexual dysfunction, this is improved following treatment with intravestical Hyaluronic Acid with a sustained effect for 12 months.

Abstract

The effect of intravesical instillations with Hyaluronic Acid on sexual dysfunction in women with recurrent urinary tract infections (RUTI).

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Objective:

To determine whether sexual dysfunction in women with recurrent urinary tract infections (RUTI) improved following treatment with intravesical Hyaluronic Acid (HA) instillations.

Study Design:

Ethical approval was obtained for a prospective study to be performed. Patients referred for bladder instillations to treat RUTI, and who were sexually active, were recruited to the study. A selection of validated questionnaires (ICIQ-UI, ICIQ-VS, FSDS-R, ICIQ-FLUTS, O'Leary/Sant and PGI-I) were completed at baseline, three, six and 12 months after initiation of treatment with bladder instillations. Treatment consisted of weekly bladder instillations with a preparation containing HA for four weeks then monthly for two further treatments. Results were populated in SPSS for statistical analysis and statistical significance was powered for 22 patients.

Results:

Thirty women were included in the study. FSDS-R was used to determine sexual dysfunction and showed that 57% patients with RUTI had significant sexual distress. There was a significant improvement in FSDS-R at three, six and 12 months when compared to baseline (Friedman two-way analysis $p<0.001$). ICIQ FLUTS F and I scores, O'Leary/Sant, ICIQ VS and PGI-I also showed a statistically significant improvement throughout the period of follow

up. A statistically significant, negative correlation was found between FSDS-R and PGI-I at 12 months (r= -0.468, p=0.009).

Conclusion:

We have reinforced previous work showing the association between RUTI and sexual dysfunction, and an improvement in bladder symptoms following treatment with HA. To our knowledge, this is the first study to prove an improvement in sexual dysfunction following intravesical treatment with HA which is sustained for up to 12 months.

Key words:

recurrent urinary tract infections

sexual dysfunction

hyaluronic acid

Introduction:

Recurrent urinary tract infections (RUTI) in women are common, with recurrence occurring within 3-6 months in 25-35% following an initial infection.[1] RUTI can be debilitating and have a profound effect on a woman's quality of life. Although not commonly explored in patient consultations, sexual dysfunction is reported in as many as 46% women with lower urinary tract symptoms. Salonia et al also showed that 60% of women with sexual arousal disorders and 61% of women with sexual pain disorders complained of RUTI.[2] Likewise, 60% women with RUTI are prone to suffer from secondary provoked vestibulodynia.[3]

It is believed that a deficiency of the uroepithelial glycosaminoglycan (GAG) layer of the bladder facilitates bacterial adherence, leading to recurrent infection.[4] Treatment to replenish this protective uroepithelium with intravesical instillation of the glucosamine Hyaluronic Acid (HA) has been proven to reduce the incidence of RUTI.[1, 5-7]

Sexual dysfunction associated with RUTI is likely to have many correlations with sexual dysfunction and painful bladder syndrome (PBS). In both conditions, the changes in the uroepithelium following HA treatment make women less likely to develop an infection and experience pain, even after intercourse, and consequently the cycle of negative association is broken. Hung et al showed an improvement in sexual dysfunction when associated with PBS following HA treatment in their multicentre study.[8] We hypothesise a similar effect would be seen when HA is used to treat RUTI. This study is designed to determine the number of patients with RUTI who see an improvement in their sexual dysfunction score following a course of intravesical treatment.

Materials and Methods:

Ethical approval was obtained for this prospective study (approved by the NRES South Central – Oxford A Research Ethics Committee, reference 14/SC/0112). It was calculated that 22 patients were needed to show statistical significance. This calculation was based on a background incidence of sexual dysfunction in 30% women, increasing to 60% in those with recurrent urinary tract infections.[2,9,10.] We assumed an improvement in 50% patients following treatment.

Patients referred for intravesical Hyaluronic Acid instillations to treat either bacterial or abacterial RUTI were approached about the study. All women had been seen by a Consultant Gynaecologist in the outpatient department and deemed suitable for the study. Inclusion criteria were sexually active women requiring intravesical treatment for RUTI. Any other major contributor for sexual dysfunction (eg. endometriosis, pelvic pain, pelvic inflammatory disease) were exclusions. Further demographic data was not collected for this study as patients acted as their own controls. Women were counselled about the study and written consent was obtained.

A series of validated questionnaires including ICIQ-FLUTS, ICIQ-VS, O'Leary/Sant, ICIQ-UI short form and FSDS-R were completed prior to treatment. Treatment consisted of either iAluRil® (Hyaluronic acid and sodium chondroitin sulphate, Aspire Pharma Ltd, Petersfield, UK) or Cystistat® (Sodium hyaluronate, Teva UK Ltd, West Yorkshire, UK) instillations performed weekly for four weeks and then monthly for a further two treatments.

The same battery of questionnaires were then completed at three months and six months, as well as a Patient Global Impression of Improvement (PGI-I) score. Patients were either reviewed in clinic or contacted by letter and asked to complete and return the validated questionnaires and PGI-I again at 12 months. Any women who did not complete the intended course of treatment and those who were no longer sexually active at follow up were excluded. Answers on ICIQ VS Sexual Matters Score was used to confirm sexual activity. Results were populated in SPSS Statistics 2012 (SPSS Inc. an IBM Company, Chicago, USA) for analysis. Correlations were calculated using Pearson's correlation coefficient and baseline scores were compared to follow up scores using Friedman's two-way analysis of variance by ranks.

Results:

Thirty patients were included for analysis. The mean age of patients was 39 years (SD 13.32). Thirteen patients received treatment with Cystistat® and 17 received iAluRil®.

Median scores were calculated for each validated questionnaire and the probability of change over the course of treatment was calculated using Friedman non parametric paired valuables. Full results are shown below in Table I.

Using FSDS-R scores as an assessment of sexual dysfunction (possible score range 0 to 52), we found that at baseline the median score in our population was 17 (IR 27.25). There was a significant fall in this score at all points of follow up although the median score at 6 months was higher than 3 months. When asked at 12 months, the median score had dropped to 1.74 (IR 19.41). This is shown in Graph I along with the change in ICIQ-VS Sexual Matters score.

Analysing the data for individual patients showed a similar pattern; eight patients (27%) reported an FSDS-R score of zero at baseline, indicating the absence of any sexual distress. The score for these patients did not change throughout follow up. Of the remaining patients, 73% (16/22) had some reduction in their FSDS-R score at 6 months. 12 month follow up data was available for 13 of these patients and 61% of them had a reduction in their FSDS-R score compared to baseline.

Using an FSDS-R score $\geq$11 to discriminate between women with and those without severe sexual distress[11], 57% had sexual distress at baseline. Although not powered for significance, looking at these 17 patients, the change in FSDS-R scores was markedly different from baseline to 12 months. The median score in this group fell from 31.47 to 15.21 at baseline and 12 months respectively.

The mean PGI-I score showed a gradual improvement in patients' global impression of symptoms over the period of follow up. The improvement in PGI-I with time was statistically significant between three months and 12 months (p=0.001).

Pearson's correlations were performed on all our variables. A statistically significant negative correlation was found between FSDS-R and PGI-I at 12 months (r= -0.468, p=0.009). This suggests that a positive impact on sexual dysfunction following treatment plays a part in women feeling better overall. This was reinforced by a strong positive correlation seen between the effect on quality of life score in the ICIQ-VS questionnaire and FSDS-R at 12 months (r=0.748, p<0.001).

There was a strong positive correlation between ICIQ VS Sexual Matters score and FSDS-R (r=0.833, $p<0.001$) with an associated negative correlation to PGI-I score (r= -0.521, $p=0.003$). Although the change in ICIQ VS Sexual Matters score was not significantly lowered throughout the period of follow up, the correlation between a lower Sexual Matters score and improved PGI-I is statistically significant. A negative correlation was found between age and PGI-I (r= -0.415, $p=0.025$).

There was a negative correlation noted between PGI-I and O'Leary/Sant problem and symptoms scores (r= -0.569, $p=0.001$ and r= -0.473, $p=0.008$ respectively) at 12 months following treatment. The link between lower urinary tract symptoms and sexual dysfunction was shown in a moderate positive correlation between FSDS-R and O'Leary/Sant problem score (r=0.408, $p=0.025$).

Comments:

This study reinforces previous work showing a positive correlation between sexual dysfunction and lower urinary tract symptoms, defined by the FSDS-R and O'Leary/Sant problem score respectively.[2] Over half of our study population had significant sexual distress (defined as an FSDS-R score ≥11)[11] at baseline and we present clear evidence that treatment for RUTI with intravesical HA significantly improves both urinary symptoms and associated sexual dysfunction. Twenty seven per cent of patients did not report any associated sexual dysfuntion.

Almost three quarters of patients with sexual dysfunction at baseline found some improvement, however slight, at six months following treatment. The reason for this improvement is not completely understood but there are several schools of thought. It has been shown that pelvic pain is reduced following HA instillations when used for painful bladder syndrome.[7] Any pain experienced in consequence to recurrent infection would also be improved, which in turn could impact on sexual function.

Given that the full course of HA instillations lasted only 6 weeks, the sustained improvement in symptoms until the end of our study period, one year from the start of treatment, suggests there may be more than a physical effect on the GAG layer involved. It is possible that the deficiencies within the GAG layer are replenished and the cycle of recurrent infection is broken. Conversely, it may be the psychological impact of treatment that results in a sustained effect. This sustained improvement was also seen in scores reflecting urinary symptoms and quality of life, reinforcing previous work.[1,5,6]

A study by Crisp has shown that women with sexual dysfunction, as defined by their FSDS-R score, do better if they have a positive coping strategy.[12] They define this as implementing a response to a stressful situation, either by avoiding the situation, regulating it, or changing the emotion attached to the situation. This could partially explain the improvement in sexual function noted in our study. Treatment with HA has a positive effect on urinary symptoms and the avoidance of recurrent infection as a stressor could be deemed a coping strategy. Women will also receive emotional support when attending for bladder instillations, but this does not explain the sustained improvement 10 months after treatment was complete.

Renard et al showed that 61.9% women with RUTI exhibited a degree of depression when using the Hospital Anxiety and Depression and Leicester scales.[13] Being referred for HA instillations may decrease concomitant anxiety knowing that a treatment is available. As treatment improves urinary symptoms, anxiety may lessen further. Mental and sexual health are inextricably linked and a general improvement in affect can improve sexual function.[14] We hypothesise that this general improvement in mood and anxiety may play a part in improving sexual function for women with RUTI. A supporting factor for this theory is the continued improvement in sexual dysfunction over time. A continued improvement in lower urinary tract symptoms will have a gradual improvement in patients' general mood, affect and anxiety. This could explain the more dramatic change between baseline and 12 months over baseline and 3 months. A similar effect was shown following endometrial ablation for heavy menstrual bleeding in perimenopausal women, where the mean FSDS-R score was reduced from 13.6 to 9.7 ($p<0.001$) before and 6 months after treatment.[15]

During the planning stages of the study we had not considered the role of mood and depression associated with RUTI and it's impact on sexual dysfunction. We hypothesise this

connection but intend to include a depression and anxiety scale to assess patients' psychological health for any future work. We therefore consider this a feasibility and pilot study and hope to further our work incorporating this new theory.

We believe that this study is the first to look directly at the effect of intravesical HA treatment on sexual dysfunction associated with RUTI. It is powered for statistical significance (n>22) and validated questionnaires were used. We acknowledge that there were some limitations to the study; there is no specific validated questionnaire for assessing RUTI. We therefore utilised the PGI-I scale which has been validated for stress urinary incontinence[16], prolapse[17] and detrusor overactivity[18] but we accept that it is not validated for use in RUTI. Further limitations include the limited sample size. We used a single-arm study design and the sample size was small, however it was powered for significance. There was a 30% drop out for 12 month follow up data. Long term follow up of patients proved very difficult, particularly as many had been discharged following treatment. Some patients had moved area and could not be contacted, others did not want to complete the lengthy questionnaires again. We appreciate that many of the questions probe into sensitive issues for this group of women and repeating the questionnaires four times may be distressing.

The length and number of questionnaires included made the risk of missing data high. Given the scoring system for each questionnaire, if a patient missed one component of the question, it was not possible to generate an accurate score. As the missing data was sporadic, Little's Test was performed. A significant result of 0.89 proved that data was missing completely at random (MCAR) and therefore median calculations for scores could be used. 11 patients did not complete 12 month follow up data, but Little's Test was still significant allowing us to perform statistical analysis.

We accept that using two different preparations for intravesical treatment has introduced some dis-homogeneity. iAluRil contains two active components, 800mg/50ml Sodium Hyaluronate (1.6%) plus 1g/50ml Sodium Chondroitin Sulfate (2%). Cystistat contains only Sodium Hyaluronate at a lower concentration of 40mg/50ml. Both preparations were used routinely in the Trust and two Consultants were involved with recruitment to the trial and had personal preferences for treatment. This was however a pragmatic study, and aimed to look at the effect of intravesical treatment for RUTI on associated sexual dysfunction. Previous work has shown both preparations to be effect for treating RUTI.

Patients with bacterial and abacterial RUTI were included, and as such many patients never had a positive urine dip test, or midstream urine culture. We therefore did not measure the number of confirmed infective episodes experienced by patients, but chose to use a symptomatic score questionnaire instead, comparing urinary symptom scores (ICIQ-FLUTS, ICIQ-UI) and PGI-I as a marker of improvement.

In conclusion, bladder instillation with HA for RUTI reduce sexual dysfunction associated with the condition. This is possibly due to a reduction in pain and lower urinary tract symptoms thereby reducing the dysfunction associated with intercourse, or by improving patient's general affect following treatment. The improvement demonstrated is statistically significant and was sustained for the 12 month follow up period.

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Figures and Tables:

Table I: Median values of validated questionnaires at baseline, 3, 6 and 12 months.

Median values (IR)*	*Baseline*	*3 months*	*6 months*	*12 months*	*Significance (p value)*
FSDS-R	17.00 (37.25)	4.50 (22.25)	7.00 (23.50)	1.74 (19.41)	**<0.001**
ICIQ-UI	4.00 (6.00)	1.00 (4.00)	1.00 (5.00)	1.17 (3.56)	**<0.001**
ICIQ-FLUTS					
F	6.00 (3.00)	5.00 (3.01)	3.50 (3.25)	3.70 (3.24)	<**0.001**
V	3.00 (3.25)	2.00 (3.20)	2.00 (2.25)	2.00 (1.93)	0.056
I	3.00 (4.83)	1.00 (4.00)	1.00 (3.00)	1.63 (3.89)	**0.035**
ICIQ-VS					
Vaginal Symptoms	9.01 (8.5)	6.00 (7.25)	4.78 (4.5)	6.00 (7.72)	**<0.001**
Sexual Score	19.00 (40.5)	13.00 (31.03)	11.00 (30.25)	7.94 (29.33)	0.333
QOL	3.50 (6.25)	2.33 (4.66)	1.00 (3.25)	1.49 (3.14)	**0.017**
O'Leary/Sant					
Symptoms	9.21 (5.25)	6.00 (3.00)	6.00 (5.25)	8.36 (5.81)	**<0.001**
Problems	7.97 (7.25)	4.00 (6.00)	3.00 (5.25)	4.00 (4.32)	**<0.001**
PGI-I	N/A	5.73 (1.25)	6.00 (1.21)	6.25 (1.82)	**0.001**

* Interquartile range

Graph I: Showing improvement in ICIQ-VS Sexual Matters and FSDS-R scores over the course of follow up.