Author’s response to reviews

Title: Sodium hyaluronate and chondroitin sulfate replenishment therapy can improve nocturia in men with post-radiation cystitis: results of a prospective pilot study

Authors:

Mauro Gacci (maurogacci@yahoo.it)
Omar Saleh (os11nov@hotmail.com)
Claudia Giannessi (cGiannessi@yahoo.it)
Beatrice Detti (beatrice.detti@aouc.unifi.it)
Lorenzo Livi (Lorenzo.livi@unifi.it)
Eleonora Monteleone Pasquetti (flowerle@tiscali.it)
Tatiana Masoni (tatim@tiscali.it)
Enrico Finazzi Agro’ (efinazzi@tin.it)
Vincenzo Li marzi (vlimarzi@hotmail.com)
Andrea Minervini (andreamine@libero.it)
Marco Carini (carini@unifi.it)
Stavros Gravas (sgravas2002@yahoo.com)
Matthias Oelke (Oelke.Matthias@mh-hannover.de)
Sergio Serni (sergio.serni@unifi.it)

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Author's response to reviews:

Reviewer 3: Ahmed M El-Zawahry

Thank you for your revision. All changes are listed in the manuscript.

1- Authors elaborated on prostate cancer and treatment in the introduction. The main topic of the study is radiation cystitis symptoms and nocturia which should be the main topic in the introduction. I was expecting to read about radiation cystitis symptoms including nocturia and how bothersome to the patients.

RE : Thanks for your revision. We treated prostate cancer and radiotherapeutic treatment in order to underline the relation between radiotherapy and nocturia. However we agree with your clever observation, a better description about nocturia and patients’ QoL would have been necessary. As you requested we added a paragraph that explain better how nocturia affect patients’ QoL.

2- in line 67, the statement about using HA and CS to treat bladder pain..., a reference is needed to support their statement.

RE: Thanks for your observation. A reference is needed. We added the reference in the manuscript.

3- Again it is not clear to me why the authors described the radiation treatment for prostate cancer?
RE: Thanks for your comment. Since urinary symptoms may be related to the type of radiation therapy scheme adopted, for clarity we decided to include a description of the treatment. However, as you rightly suggest, we have streamlined the radiotherapic treatment section.

4- Radiation cystitis has many bothersome symptoms. The authors used tools to measure all the symptoms, why did not they report on other symptoms including frequency, urgency, pain etc...

RE: Thanks for your clever remark. We enrolled 23 patients that had radiotherapy for prostate cancer and reported radiation cystitis. All patients received complete ICPI/ICSI validate questionnaire. We collected all questionnaire data, than we performed a sub analysis focused only on patients with nocturia (18 patients) as the aim of our study was to evaluate the impact of HA and CS on nocturia in patient that had radiation treatment.

6- This is a very limited number of patients with no enough compelling data to draw a conclusion.

RE: Thanks for your comment. We agree with you. Ours is a pilot study. In the conclusion we emphasized that more RCT’s are needed to confirm our data. Moreover we modified conclusion as you advice. Here below the conclusion modified:

‘In conclusion, our pilot study demonstrated that bladder instillation with HA and CS is a safe treatment in post radiation bladder cystitis. Patients after Ialuril® instillation reported a statistically significant reduction in symptom/bother nocturnal voiding frequency, even if the overall improvement due to the medication vs. spontaneous recovery must be confirmed by placebo controlled trials, including further assessment tools such as cystoscopy and histological evaluation.’

5- Although the authors showed statistically significant difference in ICSI-Q3 and ICPI-Q2 however it does not appear that it is translated to clinically relevant since only 56 of patients showed improvement (very close to placebo effect)

7- In the conclusion. I do not agree that having a success of 56 % would be considered effective treatment. I believe that the data prove that the treatment is safe but not effective.

RE: I agree with you. We have underlined this relevant limit in the text: “to better understand the timing of the response to treatment with Ialuril, and to measure the difference between spontaneous recovery of urinary function vs. treatment related clinical effect, a randomized, placebo controlled trial, with several scheduled symptoms assessments and adequate follow up time is needed”

Than as before mentioned we modified the conclusion: ‘In conclusion, our pilot study demonstrated that bladder instillation with HA and CS is a safe treatment in post radiation bladder cystitis. Patients after Ialuril® instillation reported a statistically significant reduction in symptom/bother nocturnal voiding frequency, even if the overall improvement due to the medication vs. spontaneous recovery
must be confirmed by placebo controlled trials, including further assessment tools such as cystoscopy and histological evaluation.’

Thank you very much for all suggestions to improve the overall quality of the manuscript.

Level of interest: An article of limited interest  
Quality of written English: Acceptable  
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Reviewer 1: Nissrine A. Nakib

Thank you for your revision. All changes are listed in the manuscript.

This is a very interesting concept and we are always looking for something to help these often very bothered patients. I think what would really help would be to include cystoscopic findings with these patients if available. It would have also been nice to have some of these questionnaires from before their radiation to somewhat be able to more certainly attribute the symptoms to radiation.

Furthermore 3 months after XRT is not a very long time and it could be that with additional time some of the symptoms would have resolved on their own even if they had not received the treatment. The number is so small and the difference although statistically significant may not be as clinical significant. I think if the conclusion could be changed to say that the evidence is not very conclusive but so far the treatment seems promising and that further randomized studies with correlation between cystoscopy, symptoms and perhaps even pathological findings on biopsy would make for a much stronger argument to use this treatment.

RE: Thanks for your very clever comment. We chose to analyse the immediate period after radiotherapy in order to investigate the early symptoms/bother. Obviously our pilot study is not suficent to determinate the timing of the response to Ialuril treatment. The only result the we assessed is that a percentage of patients treated with Ialuril reported an improvement of symptoms and quality of life. As you rightly emphasizes, these aspects are certainly limitations and our conclusion have to be less categorical so as you suggest we modified the conclusion as reported: ‘In conclusion, our pilot study demonstrated that bladder instillation with HA and CS is a safe treatment in post radiation bladder cystitis. Patients after Ialuril ® instillation reported a statistically significant reduction in symptom/bother nocturnal voiding frequency, even if the overall improvement due to the medication vs. spontaneous recovery must be confirmed by placebo controlled trials, including further assessment tools such as cystoscopy and histological evaluation.’

Thank you for your revision and your approval.
My primary concern about this paper is that subjects are included based on the fact that they have “symptomatic cystitis” (which is a troublesome diagnostic term already) and then a sub-analysis was done on those with nocturia. By this stepwise inclusion, it is already obvious that this study was not designed to monitor this endpoint. Rather, the appropriate design would be to identify those patients that had RT, then query for nocturia.

RE: Thanks for your analysis. Your observation is correct in fact we enrolled 23 patients with radiation cystitis. All patients received complete ICPI/ICSI validate questionnaire. We recorded all questionnaire items, than we performed a sub-analysis focused only on patients with nocturia (18 patients). Than as you rightly suggest we modified the term symptomatic cystitis in ‘urinary symptoms due to radiation cystitis’

Minor Essential Revisions

Please define “symptomatic cystitis”- is that lower urinary tract symptoms? Based on what scale? (line 75)

RE: Thanks for your comment. We wanted to emphasize the fact that the patients reported bladder pain syndrome due to radiation therapy, but as you highlight might have been better to use the term ‘urinary symptoms due to radiation cystitis’. We changed it in the manuscript.

Please cite a reference for the instillation recipe and protocol. (lines 80-82 and 102-106) The recipe for the solution is redundant and does not need to be re-stated twice. Regardless, if this is not a published protocol, please state so. Are there any animal studies?

RE: Thanks for the specification. About to the instillation protocols adopted we mentioned in the manuscript we applicate it only ‘according to the indication and schedule reported in the package leaflet of the manufacturer’. However, in the sentence we denoted it better as requested.

About the recipe for the solution we agree with you, so we removed the drugs concentration repetition in the ‘Hyaluronic acid and chondroitin sulfate administration and assessment of cystitis and nocturia’ section’.

Please address why LUTS and nocturnal voiding frequency are evaluated with the ICSI/ICPI rather than the AUA-SI or other more widely accepted tool outside the interstitial cystitis field. The authors comment that the ICSI/ICPI is one of the “most accurate tools to identify the most relevant voiding and pain symptoms due
to bladder pain” however the outcome of interest is nocturnal voiding episodes. (line 110) Please verify that the ICSI/ICPI is validated to “diagnose,” not just “monitor” symptoms/problems. Is this the only survey that was administered to this patient population?

RE: Thanks for the comment: one of the update definition is ‘to date, ICSI and ICPI are recognized among the most reliable and valid instruments to identify the most prominent voiding and pain symptoms in patients with BPS/IC’ (Giannantoni A. Patient-Reported Outcomes in Bladder Pain Syndrome: Qui Auget Dolorem, Auget et Scientiam (As Pain Increases, So Increases Knowledge). EUROPEAN UROLOGY 61 (2012) 280–283).

As you suggest it would have been better use an updated reference. We changed it

From what I can tell, the statistical model is multivariable not “multivariate” because I do not think all of the repeated measures were all put into the model, just the baseline and end of the study survey results. confirm model type. (lines 120, 151 and 189)

Appropriate multivariable logistic model building should not just include variables because they are “significant” but rather are clinically pertinent. (line 120)

RE: Thanks for your rightly observations. We have adjusted our data exclusively for Age: other items, were analogous across the whole population. Now we have corrected in the text (multivariate analysis # age adjusted model), and in the discussion we have underlined: “age adjusted analysis, demonstrating that elderly men with the worst nocturnal voiding symptoms are those with poorer outcomes after instillation therapy”

Please define “grade 2 toxicity” (line 132)

RE: Thanks for your precise comment. We adopted RTOG adverse event reporting (http://www.rtog.org/researchassociates/adverseeventreporting/acuteradiationmorbiditypsoringcriteria.aspx):’frequency of urination or nocturia which is less frequent than every hour’. We add the reference as you suggest

I am confused by lines 139-140: These lines suggest that they treated the patients that had no nocturia at baseline. Is that correct?

RE: Thank you for your clever observation. We wrote: ‘At the end of treatment, men without nocturia at baseline continued to be without nocturia: therefore, these 5 men were excluded by further statistical analyses. We enrolled 23 men after radiotherapy with BPS. All 23 patients have been treated with bladder instillations. We collected all questionnaire data (‘patients with symptoms due to radiation cystitis underwent intravesical administration of HA and CS…. all patients were asked to complete the Interstitial Cystitis Symptom Index and Problem Index.’) than we analyzed only the impact of treatment regarding nocturia according with the aims of our study. To be more clear we corrected the sentence as you underlined in ‘At the end of bladder instillation treatment, men without nocturia at baseline continued to be without nocturia: therefore, these 5
men were excluded by further statistical analyses’

I question the validity of using the total ICSI and total ICPI scores- this is a survey for interstitial cystitis. Is it validated in radiation cystitis populations? (lines 146-148)

RE: Thanks for you smart remark. ICSI/ICPI is useful to identify and measure Bladder pain syndrome irrespective to the causes. In the lines 146-148 we wanted to analyze the correlation between the values of nocturia items and total questionnaire score pre and post treatment (ICSI and ICPI) not to suggest an strictly indication to use ICPI/ICSI in patients that had radiotherapy.

Figure 1: The figure should be able to stand on its own. Please show p-values on the figure (not refer to it in the text). Also, the y-axis is not 95% CI, but score value for each respective domain. Done it. Thank you.

Table 1: Please label “end point” as Week 12. The table is sparse and actually a bit confusing. If there are no subjects who had baseline nocturia=1, remove that row, etc. There is no need to have Week 12 columns of 4 and >=5. The information from line 294 should be able to be integrated into the table. Done it. Thank you.

Table 2: Similarly lines 297-298 should be able to be integrated into the table in a standard fashion. Done it. Thank you

Table 3: This is not a very informative table. Would remove this table or at least remove all the 0 (0%) results. Very difficult to look for what is important. Lines 302-303 are redundant from the table title. Done it. Thank you

Type-o’s/word choice errors: Line 131: intermediate risk Lines 137 & 139: remove “about”

Done it. Thank you

If you adjust for a variable, then it can’t correlate with the outcome in that same model.

Line 151-153: "At age-adjusted multivariate analyses, both age and baseline ICSI-Q3 correlated with post-treatment ICSI-Q3 (r=0.293, p=0.011 and r=0.970, p<0.001, respectively)"

RE: Thanks for your comment. As reported before, we have adjusted our data exclusively for Age: other items, were analogous across the whole population. Now we have corrected in the text (multivariate analysis # age adjusted model), and in the discussion we have underlined: “age adjusted analysis, demonstrating that elderly men with the worst nocturnal voiding symptoms are those with poorer outcomes after instillation therapy”

Thank you for your revision and your approval.

Level of interest: An article whose findings are important to those with closely related research interests
The authors carried out a single-arm uncontrolled study to assess the impact of treatment (combination of hyaluronic acid and chondroitin sulfate) on nocturia. The symptom and problem of nocturnal voiding was measured with question 3 of ICSI and question 2 of ICPI, respectively. The change in symptom and problem of nocturia were assessed by paired-sample T-test of scores at baseline and post-treatment. The authors assessed the following correlations at both baseline and post-treatment: the symptom and bother of nocturia; the symptom of nocturia and ICSI total score; the problem of nocturia and total ICPI score. They also assessed the correlation of post-treatment and baseline symptom of nocturia, and finally the correlation of post-treatment and baseline problem of nocturia. The authors concluded by running two multivariable logistic regression models, the first adjusting for age, baseline symptom of nocturia, and baseline ICSI total score; and the second adjusting for age, baseline problem of nocturia, and baseline ICPI score. While it appropriate to utilize paired-sample t-test to test for change in nocturia from baseline to post-treatment, there are changes that should be made to strengthen this paper.

1) The authors should focus on estimation rather than inference in terms of change in score. The authors should report the estimate, including the 95% confidence interval to guide their conclusion regarding a randomized, controlled trial.

RE: I agree with you that fur further RCTs, the 95% CI could be determinant. However, a RCT on the use of ialuril to treat ALL the post radiation urinary symptoms could not be based on the 95%CI of EXCLUSIVELY the nocturia item. Our statisticians are working on a model based on the 95% CI of ALL ICSI and ALL ICPI Items. The topic of the present manuscript is NOCTURIA: therefore, we have not included the 95%CI in this paper.

2) Based on their study design, the authors should reword their conclusion since improvement after treatment is not equivalent to the treatment reducing the symptom. It is reasonable that if patients were not given the treatment, their symptoms would have also improved.

RE: Thanks for your observation. We modified the conclusion as you suggest:

In conclusion, our pilot study demonstrated that bladder instillation with HA and CS is a safe treatment in post radiation bladder cystitis. Patients after Ialuril® instillation reported a statistically significant reduction in symptom/bother nocturnal voiding frequency, even if the overall improvement due to the
medication vs. spontaneous recovery must be confirmed by placebo controlled trials, including further assessment tools such as cystoscopy and histological evaluation.’

3) The purpose of assessing and reporting the correlation between every variable is unclear.
RE: Thanks for your rightly observations. The term “multivariate” is a mistake. We have adjusted our data exclusively for Age: other items, were analogous across the whole population. Now we have corrected in the text (multivariate analysis age adjusted model).

4) Although the authors included limitations to their study, it would be beneficial to discuss these limitations in terms of possible bias to their results.
RE: Thanks for your remark. As you suggest we should have been more clear to describe our study’s limits. After your advise we modified the limits section as reported:

Our small sample size could be considered satisfactory for a “pilot study design”; however, to better understand the timing of the response to treatment with Ialuril, and to measure the difference between spontaneous recovery of urinary function vs. treatment related clinical effect, a randomized, placebo controlled trial, with several scheduled symptoms assessments and adequate follow up time is needed.

5) Regarding the multivariable logistic model:
a. it is unclear what the outcome was defined as. Is this the post-treatment score based on a cutpoint?
b. it is also unclear why the baseline score of the individual question and the total score were both adjusted for in the model, as one component consists of the other.
RE: Thanks for your comment. As previously stated we have adjusted our data exclusively for Age: other items, were analogous across the whole population. Now we have corrected in the text (multivariate analysis age adjusted model), and in the discussion we have underlined: “age adjusted analysis, demonstrating that elderly men with the worst nocturnal voiding symptoms are those with poorer outcomes after instillation therapy”

c. with a sample size of 18 patients for the majority of the analyses, multicollinearity would be a concern by incorporating three variables in this model.
d. it is unclear what estimates are being reported in the multivariate analyses (line 152).
e. the author reported the covariates included in the multivariable analyses in the abstract but not in the manuscript, it should be mentioned in both locations for clarity.
RE: Thanks for your specification. As previously specified: We have adjusted our
data exclusively for Age. We also have modified the abstract: ‘Nocturnal voiding frequency was assessed by item 3 (Q3) of the Interstitial Cystitis Symptoms Index (ICSI) and item 2 (Q2) of the Interstitial Cystitis Problem Index (ICPI). Data were analyzed with paired-samples T-test and adjusted for age’

6) The first half of Table 3 summarizes the data being reported in Table 1, and therefore does not need to be reported in both ways.

RE: Thank you for your observation. As you stresses, the table 3 (the first half) shows data that can be extrapolated from Table 1. Table 3 was prepared in that way to highlight the comparison at a glance between ICSI Q3 and ICPI Q2 regard patients improving, worsening or stable after treatment. However as you suggest we have streamlined the table 3 to make it easier to read.

Thank you for your revision and your approval.