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14. ABSTRACT

The purpose of this study was to evaluate the efficacy of intranasal oxytocin on bladder nociception in a cohort of patients with interstitial cystitis (IC). We hypothesized that patients with IC are more likely to experience treatment responses as defined by global response assessment (GRA) scores when they receive intranasal oxytocin as opposed to when they receive intranasal saline. Secondary outcome measures included a verbal pain report (VPR; 0-10 with 0 being no pain and 10 being the worst possible pain), a verbal anxiety report (VAR; 0-10 with 0 being no anxiety and 10 being the worst possible anxiety), number of voids since last contact with an investigator, and interim medications used for pain control or anxiety. Compared to saline administration intranasal oxytocin did not significantly decrease anxiety, pain or the number of voids reported by participants.

15. SUBJECT TERMS
Interstitial cystitis, oxytocin, intranasal, bladder, pain, anxiety

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1. INTRODUCTION

The purpose of this study was to evaluate the efficacy of intranasal oxytocin on bladder nociception in a cohort of patients with interstitial cystitis (IC). We hypothesized that patients with IC would be more likely to experience treatment responses as defined by global response assessment (GRA) scores when they received intranasal oxytocin as opposed to when they received intranasal saline. Our primary outcome measure was the GRA score, which was collected at 6 and 24 hours post drug or placebo administration. This is a seven-point symmetric scale previously validated for use in IC studies in which patients are asked relative to baseline (i.e. over the last 6 hours for purposes of this study), are you markedly worse, moderately worse, slightly worse, no change, slightly improved, moderately improved, or markedly improved. Moderate or marked improvement was defined as a treatment response. Secondary outcome measures included a verbal pain report (VPR; 0-10 with 0 being no pain and 10 being the worst possible pain), a verbal anxiety report (VAR; 0-10 with 0 being no anxiety and 10 being the worst possible anxiety), number of voids since last contact with an investigator, and interim medications used for pain control or anxiety. The VPR and VAR were assessed for the current point in time and the interim time period since last investigator-initiated contact. Participants were asked to record their number of voids and concomitant medication use in a diary so that the results could be accurately reported to the investigators.

2. KEYWORDS

Interstitial cystitis
Oxytocin
Bladder
Global response assessment
Verbal pain report
Verbal anxiety report
Void

3. ACCOMPLISHMENTS

- **What were the major goals of the project?**

The major goal of this project was to evaluate the efficacy of intranasal oxytocin in relieving bladder pain in a cohort of patients with interstitial cystitis.

- **What was accomplished under these goals?**

Our primary outcome measure was the global response assessment (GRA) score, which was collected at 6 and 24 hours post drug or placebo administration. This is a seven-point symmetric scale previously validated for use in IC studies in which patients are asked relative to baseline (over the last 6 hours for purposes of this study), are you markedly worse, moderately worse, slightly worse, no change, slightly improved, moderately improved, or markedly improved. Moderate or marked improvement will be defined as a treatment response.[1-2]

Secondary outcome measures included a verbal pain report (VPR; 0-10 with 0 being no pain and 10 being the worst possible pain), a verbal anxiety report (VAR; 0-10 with 0 being no anxiety and 10 being the worst possible anxiety), number of voids since last contact with an

investigator, and interim medications used for pain control or anxiety. The VPR and VAR were assessed for the current point in time and the interim time period since last investigator-initiated contact.

For purposes of comparison with our previous studies and those of others related to subjects with pain, we administered a series of questionnaires that characterized the subjects' demographic information, health history, pain-related symptoms, health status perceptions and hypervigilance.

Figure 1 below shows mean GRA scores obtained 6 and 24 hours post oxytocin or saline administration. There was no significant difference in GRA scores obtained after patients received oxytocin compared to when they received saline. Furthermore, neither oxytocin nor saline produced moderate or marked improvement, which would have defined a treatment response.

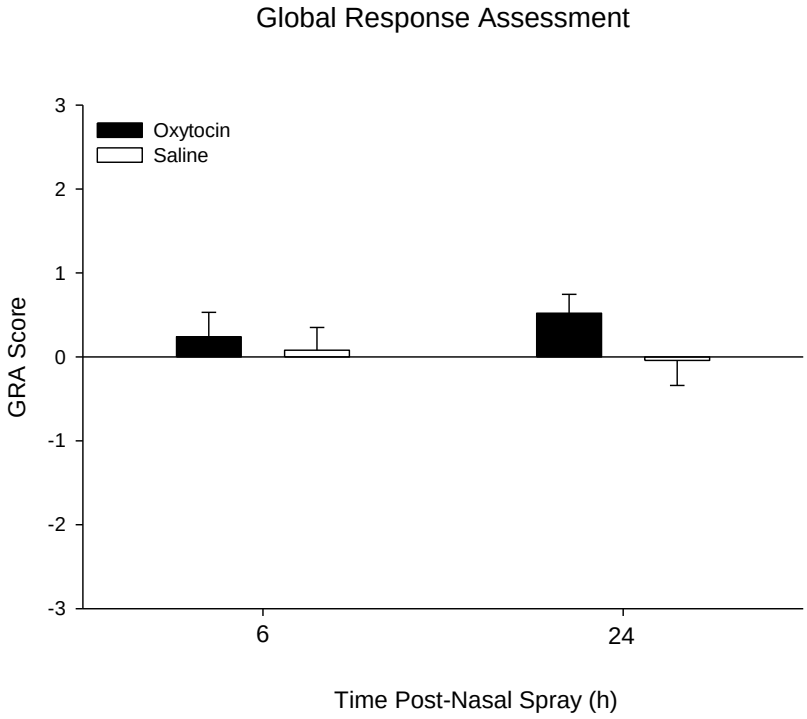

Figure 1: GRA Score. GRA scores were not significantly different either 6h (t=0.403; p=0.688) or 24 h (t=1.514; p=0.137) after saline or oxytocin administration. N=25.

Secondary response measures that were collected and analyzed for possible treatment effects were the VPR, VAR and number of voids. In Figure 2 below, it is clear that both the VPR (left panel) and the VAR (right panel) both decreased after patients intranasally administered oxytocin and saline. However, there was no significant difference in improvement in these measures post-oxytocin compared to post-saline. Similarly, voiding behavior was not different after intranasal oxytocin compared to intranasal saline. Figure 3 shows total number of voids in the first 6 hours (left panel) and over the entire 24 hour (right panel) evaluation period.

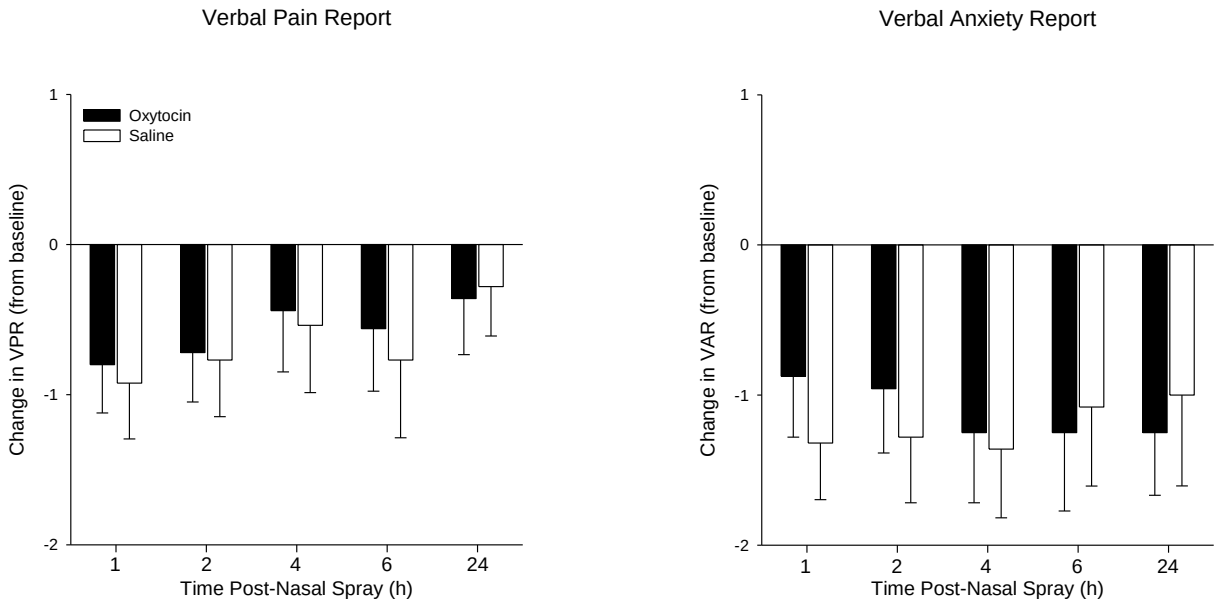

Figure 2: Secondary Outcome Measures. VPR (left panel) and VAR (right panel) were assessed 1, 2, 4, 6 and 24 hours after oxytocin and saline administration. Although pain and anxiety reported by patients did decrease, this effect was apparent regardless of the type of intranasal spray administered. No significant differences were found (N=25).

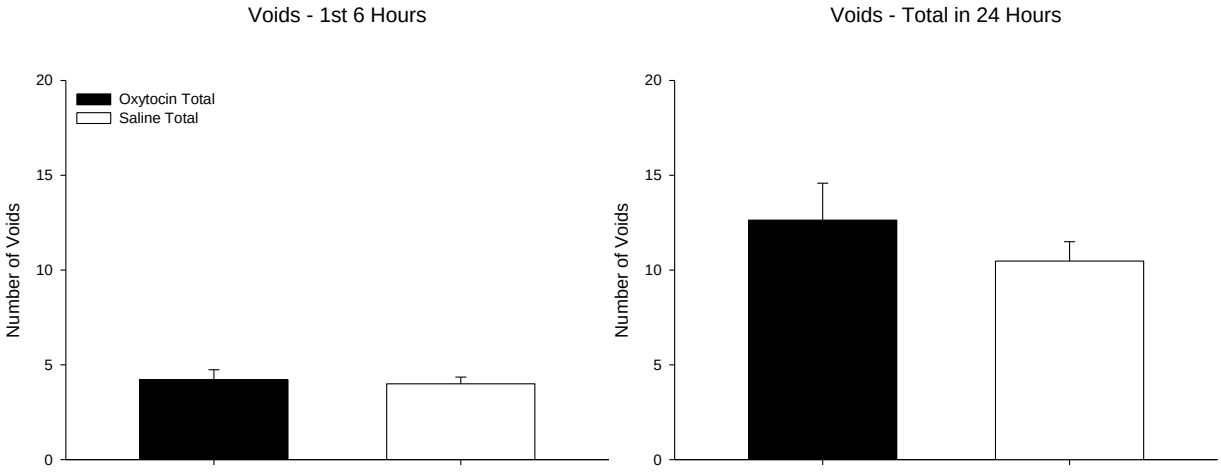

Figure 3: Voiding Behavior. The total number of voids in the first 6 h and over the entire 24 h experimental period was calculated. Patients' voiding was similar at both time points regardless of the intranasal substance received, and no significant differences were observed over the first 6 h (t=0.327; p=0.745) nor over 24 h (t=0.980; p=0.333). N=23-24.

General demographic and health history information were gathered using a traditional medical history and custom form. The O'Leary-Sant IC Symptom and Problem Index[3] was utilized to assess urinary symptoms. The Center for Epidemiologic Studies - Depression Scale (CES-D) was administered to assess symptoms of depression.[4-5] The McGill Pain Questionnaire (MPQ), a self-report instrument that measures the sensory, affective, and intensity dimensions of pain, was also administered.[6-8] These data are shown in Tables 1 and 2.

Table 1. Characteristics of the Participants in the Study Sample

Characteristic	
Age (mean ± SD)	45.80 ± 12.63
Sex (n, %)	
Women	25 (100)
Men	0 (0)
Ethnic background (n, %)	
Caucasion	23 (92)
African-American	1 (4)
Native-American	1 (4)
Education in years (mean ± SD)	13.84 ± 1.99
Comorbidities (n, %)	
TMJ/Facial Pain	9 (36)
Fibromyalgia	8 (32)
Chronic Fatigue Syndrome	9 (36)
Back Pain	13 (52)
Joint Pain	9 (36)
Chronic Headache	8 (32)
Depression	12 (48)
IBS/ GI Pain	10 (40)
Premenstrual/Menstrual Pain	14 (56)
Bladder Pain	25 (100)

Table 2. Questionnaire Data from the Participants in the Study Sample

Questionnaire	Score (mean ± SD)
Short-Form McGill Pain Questionnaire	
Sensory Pain Rating Index (range 0-33)	15.12 ± 5.90
Affective Pain Rating Index (range 0-12)	5.40 ± 3.12
Total Pain Rating Index	20.52 ± 8.51
Evaluative Overall Intenstity of Pain Experience (range 0-5)	3.04 ± 0.88
IC Symptom and Problem Questionnaire	
IC Symptom Index (range 0-20)	13.36 ± 4.95
IC Problem Index (range 0-16)	10.92 ± 4.06
Center for Epidemiologic Studies Depression Scale (range 0-60)	23.96 ± 6.57

- **What opportunities for training and professional development has the project provided?**

This project allowed me the opportunity to design and execute a clinical trial. This was an invaluable experience. Furthermore, I was able to interact with a population of patients with chronic pain for the first time. Up to this point in my career I had only used animal models to study pain in general and interstitial cystitis specifically. To be able to speak with patients who live with this condition was a truly eye- opening experience. I gained a much better understanding of the disease itself and of chronic pain while working on this project.

- **How were the results disseminated to communities of interest?**

Nothing to Report

- **What do you plan to do during the next reporting period to accomplish the goals?**

Nothing to Report

4. IMPACT

- **What was the impact on the development of the principal discipline(s) of the project?**

Unfortunately there was no apparent beneficial effect of the intranasal oxytocin in the present study. It may be that the current delivery system was ineffective in allowing the entire dose of oxytocin to reach its target and/or be absorbed completely. The volume necessary to deliver the appropriate dose of oxytocin is quite high, so it is possible that switching to a higher concentration/lower volume formulation of oxytocin would be more efficient and would allow for definitive determination of its effectiveness at relieving pain and/or anxiety.

- **What was the impact on other disciplines?**

Nothing to Report

- **What was the impact on technology transfer?**

Nothing to Report

- **What was the impact on society beyond science and technology?**

Nothing to Report

5. CHANGES/PROBLEMS

- **Changes in approach and reasons for change**

Nothing to Report

- **Actual or anticipated problems or delays and actions or plans to resolve them**

Recruitment was more difficult than initially anticipated. For this reason, a no-cost extension request for an additional 12 months of time was submitted, which allowed for completion of the study as originally proposed. No additional funds were requested for this time.

- **Changes that had a significant impact on expenditures**

Nothing to Report

- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

Nothing to Report

6. PRODUCTS

- **Publications, conference papers, and presentations**
  - **Journal publications.** Nothing to Report
  - **Books or other non-periodical, one-time publications.** Nothing to Report
  - **Other publications, conference papers, and presentations.** Nothing to Report

- **Website(s) or other Internet site(s)**
  - https://clinicaltrials.gov/

- **Technologies or techniques**

Nothing to Report

- **Inventions, patent applications, and/or licenses**

Nothing to Report

- **Other Products**

Nothing to Report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?**

  Meredith T. Robbins-no change

  Timothy J. Ness-no change

  Michael Froelich-no change

  L. Keith Lloyd-no change

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

  - The PI, Meredith Robbins, has closed two previously active NIH grants. One study was completed in June 2015, and the second study was completed in September 2015.

- **What other organizations were involved as partners?**

Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

N/A

9. APPENDICES

N/A

10. REFERENCES

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