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14. ABSTRACT
The purpose of this study is to evaluate the efficacy of intranasal oxytocin on bladder nociception in a cohort of patients with interstitial cystitis (IC). We hypothesize 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 include 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 significantly decrease anxiety reports from participants. While the difference in pain ratings between the two treatments is not statistically significant, there does also appear to be a small effect of oxytocin at reducing pain.

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

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Table of Contents

Page

Introduction……..…..4

Body……..4-6

Key Research Accomplishments……..……..7

Reportable Outcomes……7

Conclusion……7

References…….7-8

Appendices……n/a

INTRODUCTION

The purpose of this study is to evaluate the efficacy of intranasal oxytocin on bladder nociception in a cohort of patients with interstitial cystitis (IC). We hypothesize 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. Our primary outcome measure is the GRA score, which will be 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 will be defined as a treatment response. Secondary outcome measures include 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 will be assessed for the current point in time and the interim time period since last investigator-initiated contact. Participants will be asked to record their number of voids and concomitant medication use in a diary so that the results can be accurately reported to the investigators.

BODY

RESULTS

This study is a prospective placebo-controlled, double-blinded, crossover trial comparing the effect of intranasal oxytocin to intranasal saline on pain and anxiety in patients with interstitial cystitis (IC). At this time, five participants have completed both parts of the study, and the data was unblinded to allow for an initial analysis. This was done primarily to determine whether any modifications should be made to the protocol before a large number of individuals had participated. The results can be seen in the figures below. Data from one patient was excluded; she experienced a family crisis during the course of the study, which likely impacted both anxiety and pain reports, and her dataset was incomplete as a result.

Verbal pain report. Figure 1 indicates that relative to baseline, both intranasal oxytocin and intranasal saline decrease pain ratings at the 1 hour time point. Pain reports at subsequent time points are lower with oxytocin administration compared to those following saline administration. While the difference in pain ratings between the two treatments is not statistically significant, there does appear to be a small effect of oxytocin at reducing pain. VPRs at 24 hours were closer to baseline.

Preclinical studies have indicated a potential analgesic role for oxytocin in pain associated with the bladder[3,5], and it was anticipated that similar results would be seen in the present study. While no significant effect of oxytocin on pain has been observed to date, there is a trend in that direction, and a larger sample size is still needed.

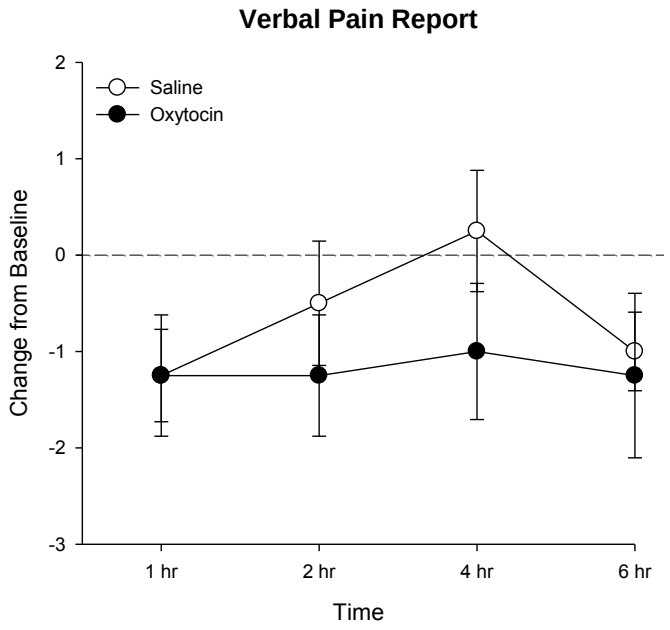

Figure 1: Verbal pain report (VPR). VPR is expressed as change from baseline, which is indicated by dashed line, during the 24 hours after either intranasal oxytocin or saline. VPR was initially decreased following both treatments, but this slight improvement in pain persisted after oxytocin. However, no significant differences were found between treatments. N=4/treatment condition.

Verbal anxiety report. As shown in Figure 2, a more robust effect of oxytocin was observed on anxiety. Again, both treatments lowered anxiety initially, but by 4 hours, VARs continued to decrease with oxytocin and were close to baseline with saline. Compared to saline administration intranasal oxytocin did significantly decrease anxiety at the 6 hour time point. No differences in the two treatments conditions were evident by the 24 hour time point.

These findings are consistent with reports of decreased anxiety behaviors in numerous animal studies[2,3,7-11]. Recent clinical studies have also reported similar anxiolytic-like effects of oxytocin[1,4,6]. As the sample size is increased, it is anticipated that this effect will become more evident.

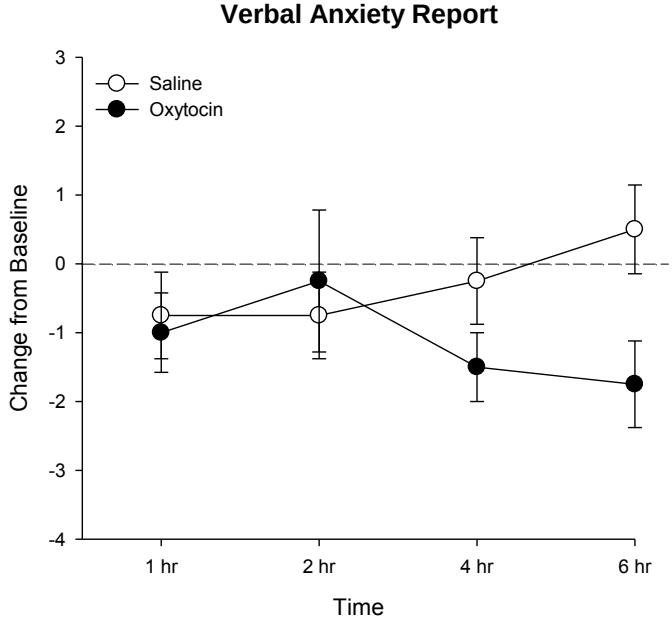

Figure 2: Verbal anxiety report (VAR). VAR is expressed as change from baseline, which is indicated by dashed line, during the 24 hours after either intranasal oxytocin or saline. Although both treatments slightly dereased VAR initially, oxytocin had a significantly greater effect at the 6 hour time point. N=4/treatment condition.

Voiding. Figure 3 indicates that the total number of voids during the first 6 hours post-treatment and the entire 24 hour period was similar following administration of saline and oxytocin. Data presented is from 3 participants; one of the four included in the other analyses had a cystectomy and empties her bladder via catheterization.

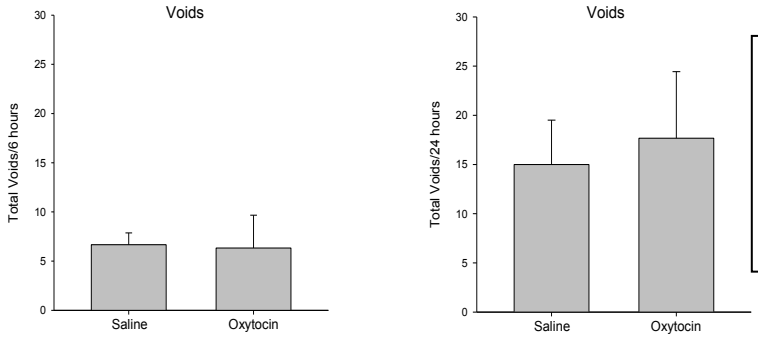

Figure 3: Total voids. The number of voids for the first 6 hours (left panel) and the entire 24 hours (right panel) were totaled for each participant. No difference in voiding was observed at either time interval. N=3/ treatment condition.

Global response assessment (GRA). The GRA scores were not markedly different between the two intranasal conditions 6 or 24 hours after treatment. The distribution of responses can be seen in the table below.

Table 1.

	6 hr		24 hr	
GRA	Saline	Oxytocin	Saline	Oxytocin
Improved	2	2	2	1
No change	1	1	2	3
Worse	1	1	0	0

PROBLEM AREAS

No significant problems have arisen during the course of the study. Two participants reported transient lightheadedness after receiving one of the intranasal substances. This was completely gone within two hours. One of these participants had some flushing four hours after the nasal spray that resolved spontaneously and required no treatment. The study monitor looked into this and concluded that none of these symptoms was associated with the intranasal oxytocin since both participants has received placebo in these instances. This was included in the third quarterly progress report in Year 1 and was also reported to the IRB.

To date, 14 participants have completed the study. Recruitment has been more difficult than initially anticipated. For this reason, a no-cost extension request for an additional 12 months of time was submitted. This would allow for completion of the study as originally proposed. No additional funds were requested for this time.

FUTURE WORK

Additional data is currently being collected and patients are continuing to be enrolled. Once 24 patients have been enrolled and completed the study, an interim analysis will take place, and a decision will be made whether to continue the study as a crossover trial or transition to a randomized, placebo-controlled, single-arm study based on patient responses and follow-up.

KEY RESEARCH ACCOMPLISHMENTS

- Intranasal oxytocin appears to be effective at lowering anxiety in IC patients.
- There is a suggestion from this small sample that oxytocin may have a slight analgesic effect as well.
- The dose used in the present study appears to be safe and is not eliciting any adverse side effects.

REPORTABLE OUTCOMES

At this time, data collection is still in progress, and there are no reportable outcomes.

CONCLUSIONS

To date, the results of the present study indicate that intranasal oxytocin may have some positive effect on pain reports (reduction in pain) in women with IC. However, this effect is not significantly different from the results obtained following intranasal saline (placebo) administration. However, there is a significant effect of oxytocin on anxiety in these patients - anxiety reports are lower following oxytocin compared to saline. Once additional patients complete the study, an interim analysis will be performed and this larger sample size will allow a more definitive conclusion about the effectiveness of oxytocin.

If the effect of oxytocin on pain is still present but not significant, it may be that the current delivery system is 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.

If the results of this study are positive, further studies would be warranted to define (1) the optimal dose and duration of effect, (2) whether oxytocin is acting in an analgesic or anxiolytic manner, (3) the exact mechanisms of analgesia or anxiolysis, and (4) whether or not peripheral oxytocin has analgesic effects in other types of nociception making it a useful agent for chronic pain syndromes other than IC.

Because the causes of IC are unknown, current treatments are aimed at relieving symptoms. These include bladder distention, bladder instillation with DMSO, oral drugs (Pentosan Polysulfate Sodium (Elmiron), aspirin, ibuprofen, tricyclic antidepressants, antihistamines, narcotic analgesics such as acetaminophen (Tylenol) with codeine or longer-acting narcotics), electrical nerve stimulation, changes in diet, cessation in smoking, exercise, bladder training, physical therapy, and surgery. Unfortunately there is no single treatment that provides relief for all patients, and some patients do not experience any improvement after undergoing multiple treatments. Some of the current treatments are invasive or have untoward side effects. Since intranasal oxytocin is safe and non-invasive, if it effectively relieves pain, this could be a significant improvement on current treatment options for IC and other chronic pain disorders.

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