

# An Experimental Single-Case Design in Effectiveness of Oxytocin on Reducing Alcohol Addiction in a Patient with Oropharyngeal Carcinoma-the Mediation Role of Difficulties in Emotional Regulation

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## Abstract

Oxytocin, due to its potential for modulation of cravings, is a possible alternative therapy for alcohol dependency. Management or cessation of alcohol use can increase the survival rates in cancers affected by alcohol abuse. The present study is an experimental single-case, reversal design study that has a multiple baselines and a 6-month follow-up. The study was conducted between January 2014 and November 2015. The patient was a 67-year-old man, known to abuse alcohol, who had a diagnosis of metastatic oropharyngeal squamous cell carcinoma and dysthymia syndrome. He was selected by a respondent-driven sampling method. The patient was treated with intranasal oxytocin in two stages and for six weeks. In the control phase, he used a placebo. The primary outcomes were the Addiction Severity Index results and changes to the Difficulties in Emotion Regulation Scale. The secondary outcome was the relationship between emotion regulation and addiction severity. The data were analyzed by the generalized estimation equation, linear mixed models (random effect model) with repeated measures, and correlation with repeated measures. Primary outcomes showed that intranasal oxytocin caused a significant decrease in addiction severity in its interaction with regulation of emotion. However, this reduction was not sustained until the follow-up stage. Secondary outcomes showed a direct relationship between the difficulty in controlling emotions and the severity of alcohol addiction. Oxytocin could decrease addiction severity by decreasing cue reactivity; thus, it could be considered an effective intervention in the field of addiction.

**Keywords:** Oxytocin, Cancer oropharyngeal, Alcohol use disorder, Depression

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## Introduction

A number of cancers are affected by smoking, alcohol and drugs use. Oropharyngeal squamous cell carcinoma (OPSCC) is a relatively rare disease that its progress is affected by alcohol and tobacco use.<sup>1</sup> Along with conventional treatments for cancer, alcohol use control can increase survival rates in these patients. In the first months of abstaining, alcohol-dependent patients often show sleep disorders, irritability, and depression, which indicate chronic activity of the stress-related pathways.<sup>2</sup>

Oxytocin hormone affects the transmission of physical signals and, due to its potential in craving modulation, is a proposed alternative therapy for alcohol abuse disorders.<sup>3</sup> From the neurobiological point of view, it has been suggested that the oxytocin social hormone can be effective for addictive behaviors such as alcohol use through the promotion of social interactions and improvement in psychological indices.<sup>4</sup> Oxytocin acts by inhibiting the effects of corticotropin-releasing factor on GABAergic interneurons in amygdala and hypothalamic nuclei.<sup>2</sup> Studies show an association between heavy alcohol consumption and lower levels of oxytocin in the brain; this process is referred to as a mechanism for changes in social behavior, response to stress, and increasing alcohol abuse.<sup>5</sup> Because oxytocin is a peptide, intranasal pathway delivery is the preferred method in clinical studies.<sup>6</sup>

Studies show that intranasal oxytocin reduces the amount of neuronal cue reactivity in brain networks, which can be associated with reduced alcohol use.<sup>7</sup> In preclinical and clinical studies, oxytocin has successfully reduced the consumption of ethanol, cocaine, and methamphetamine.<sup>8</sup> On the other hand, studies have shown that difficulties in emotional regulation with influencing on metacognition is effective on behavioral addiction like Internet Addiction.<sup>5</sup>

Although studies have been conducted on the effectiveness of oxytocin on reducing alcohol use, this intervention has not been evaluated in patients with cancers. Therefore, the aim of this study was to investigate the effectiveness of

intranasal oxytocin on the reduction of addiction severity in a patient with oropharyngeal squamous cell carcinoma.

## Case Report

The present study was a reverse A1B1A2B2C1 design with multiple baseline and six-month follow-up (Registry Code: TCTR20180511003). The patient is a 67-year-old married man who has had heavy episodic alcohol consumption for about 20 years and was selected through a respondent-driven sampling method.<sup>9</sup> during January 2014 and November 2015. Consumption of at least 24 standard drinks per week was considered as the criterion for heavy alcohol consumption. The patient, about one year ago, was diagnosed with squamous cell carcinoma by punch biopsy. He underwent radical resection of the squamous cell carcinoma of the oropharynx and, in accordance with the Union for International Cancer Control's (UICC) criteria, stage pT2, pN1. The patient received adjuvant radiotherapy and cisplatin. Five months ago, a computed tomography (CT) scan confirmed the presence of bone and lung metastases.

The patient entered into treatment process because of his heavy episodic alcohol consumption and dysthymia. Based on The International Classification of Diseases, Ninth Revision (ICD-9), he was diagnosed with alcohol use disorder (ICD-code: 303). Preliminary evaluation of the 28 days prior to the registration of the baseline included an electrocardiogram examination, blood and urine tests by a team consisting of a psychiatrist, two clinical psychologists, and a nurse.

In A1 and A2 baselines (4 weeks, 8 evaluations), only evaluations were performed with no interventions. In phase B1 (6 weeks, 12 evaluations) and B2 (6 weeks, 12 evaluations), the patient received intranasal oxytocin. In order to reduce the level of oxytocin plasma for evaluation as the second baseline, there was a 2-month interval between the B1 and A2 phases. The entire study period lasted 14 months with 44 total evaluations. The sustainability of changes was

evaluated in the form of a 6-month follow-up (C1, 4 weeks, 4 evaluations).

Oxytocin intranasal spray (Syntocinon®; Novartis, Basel, Switzerland) consisted of oxytocin plus glycerol, sorbitol, benzyl alcohol, and distilled water placed in an amber 7 mL glass. The nasal spray had a metered pump. Placebo sprays consisted of the same combination, but did not contain oxytocin. Each pump spray delivered 50 µL of Oxytocin (9 IU) or placebo. All sprays were safely kept at 4°C. The patient was provided with necessary instructions for proper use of the nasal spray and information about recording the doses in a notebook. A timer was used as a reminder. The bottles were collected at the end to assess the total amount and the used dose. The patient used the medication twice per day, before breakfast and before an afternoon snack. The dose for each administration was 18 IU (9 IUs puffs per each nostril).

In this study, a semi-structured clinical interview, Difficulties in Emotion Regulation Scale (DERS), addiction severity Index and Alcohol Use Disorders Identification Test (AUDIT) were used. All interviews were digitally recorded and copied from the recordings and coded. All study data were collected after agreement with the patient. The patient provided informed consent before the intervention and publication, and all stages of the study were based on the latest version of the Declaration of Helsinki (DoH). The data were analyzed using the generalized estimation equation 10, linear mixed

models (random effects models) with repeated measures 11, and correlation with repeated measures.  $P < 0.05$  was considered statistically significant.

The scores of the subject in the variable of total score of addiction severity index during 14 months and in the form of 44 evaluations are presented in Chart 1.

As it could be seen, the results of the generalized estimation equation (GEE) test show that there were significant decreases in the two stages of intervention (B1 and B2) ( $P = 0.04$ ). This improvement was not maintained in the follow-up stage ( $P = 0.03$ , Figure 1).

The linear mixed model showed that the decrease in addiction severity in interacting with the difficulty index in emotional regulation was significant ( $P = 0.02$ ). Repeated measures correlation (rmcorr) showed that there is a significant relationship between two indices of addiction severity and difficulty in emotional regulation ( $P = 0.01$ ).

## Discussion

This study was conducted aimed to evaluate the effectiveness of oxytocin on reducing addiction severity and improving emotional regulation. Primary outcome showed that oxytocin reduced addiction severity index and also difficulty in emotional regulation. The secondary outcome revealed a direct relationship between addiction severity and difficulty in emotional regulation.

In this regard, and in line with the primary

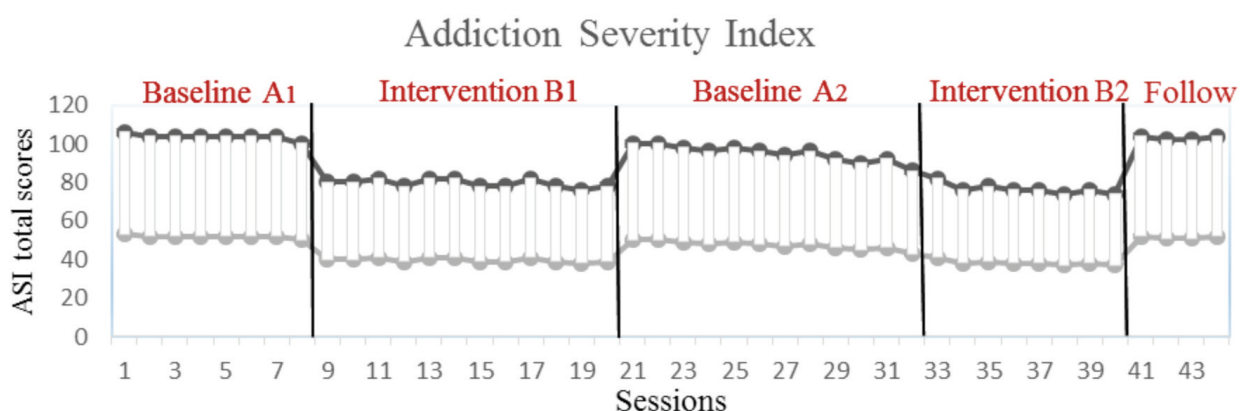


Figure 1. Score of ASI in during 44 evaluations.

outcome of the present study, the results of a study by Faehrmann et al.<sup>2</sup> showed that oxytocin, by reducing anxiety and depression, could reduce the mechanism of craving in alcohol dependent people and help the patient during the abstinence phase.

Contrary to our results, the results reported by Betka et al.<sup>3</sup> showed that, despite the effectiveness of oxytocin on interoceptive accuracy, it did not effectively reduce alcohol consumption. However, studies showed that defects in interoceptive function could explain depression syndrome.<sup>12</sup>

Another part of our findings showed that oxytocin effectively reduced depressive episodes. In accordance with our findings, the results of a study by Love et al.<sup>4</sup> showed that oxytocin, by increasing social participation and improving mental health, improved psychological indices such as depression in alcohol users. The findings of Faehrmann et al.<sup>2</sup> suggested a moderator role for oxytocin on stress-related pathways in alcohol dependent individuals, which could be used in treatment. In this regard, studies have shown that stress-related function has a significant relationship with emotional regulation.<sup>13</sup>

The secondary outcome showed that there is a significant direct relationship between difficulty in emotional regulation and addiction severity index. In line with these results, Kopera et al.<sup>14</sup> showed that long-term alcohol consumption is associated with difficulty in emotional regulation and major depressive disorder (MDD).

Ethanol consumption decreases the activity of the HPA axis, which can affect both response to stress and mood parameters.<sup>15</sup> In line with our results, Pirnia et al.<sup>16</sup> have reported a significant relationship between changes in the function of the HPA axis and depression syndrome in drug abusers.

According to the single case nature of this study, the effects of intranasal oxytocin on addiction severity index need to be repeated in a larger study. Also this study was the use of self-report scales that could have been associated with bias. It is suggested that in future studies,

biological evaluations should be used to investigate the variables. The effectiveness of oxytocin in individuals diagnosed with alcohol use disorder in the form of a randomized controlled trial can be a good route for the future studies.

## Conclusion

The results of this study showed that oxytocin caused a decrease in addiction severity in its interaction with regulation of emotion. We observed a direct relationship between the difficulty in controlling emotion and the severity of alcohol addiction. Oxytocin could be considered an effective intervention for addiction.

## Conflict of Interest

None declared.

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