**The effect of intranasal oxytocin on processing emotional stimuli during alcohol withdrawal:
A randomized placebo-controlled double-blind clinical trial**

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Abstract

Alcohol dependence is associated with difficulties in processing emotional stimuli, which can lead to interpersonal problems. The neuropeptide oxytocin has been shown to modulate the processing of emotional stimuli, however, oxytocin treatment has not yet been examined in patients with withdrawal symptoms during alcohol detoxification. The aim of the present study was to investigate the effect of oxytocin on the reading the mind in the eyes test (RMET) during a three-day period of alcohol detoxification at an addiction treatment centre in Norway. We performed a randomized, double-blind, placebo-controlled trial in 39 patients fulfilling criteria for ICD-10 diagnosis of alcohol dependence admitted for alcohol detoxification and withdrawal treatment. Participants were randomized to receive either intranasal oxytocin (24 IU) or placebo, twice daily for three days. The primary outcome was RMET performance on day 2 and day 3 of detoxification and secondary outcome was the differences in RMET scores between day 2 and day 3 of detoxification. Frequentist and Bayesian statistical inference suggested that oxytocin administration during alcohol withdrawal in alcohol-dependent patients did not improve social cognition performance, however alcohol use before detoxification significantly predicted RMET performance on day 2, but not on day 3, of withdrawal.

1. Introduction

Alcohol dependence is associated with emotional dysregulation, which can contribute to interpersonal relationship difficulties and post-treatment relapse. The processing of emotional stimuli in alcohol dependence is commonly assessed by Reading the Mind in the Eyes Test (RMET), which indicates that patients with alcohol dependence have impaired abilities to recognise positive, negative and complex emotions (Maurage et al., 2011; Nandrino et al., 2014; Thoma et al., 2013). Oxytocin is a neuropeptide and hormone primarily produced in the hypothalamus that has been proposed to exert both social and anxiolytic effects in human and non-human mammals (King et al., 2020). RMET performance has been shown to be enhanced after oxytocin administration in a healthy population (Domes et al., 2007) and in alcohol dependent individuals (Mitchell et al., 2016), although the latter finding was not replicated in a subsequent study (Radke and de Bruijn, 2015).

There is growing research interest as to whether the social and anxiolytic effects of oxytocin can be useful in treatment during different stages of alcohol use disorder in order to alleviate withdrawal symptoms, craving, and relapse (King et al., 2020). Researchers have investigated RMET performance in non-treatment seeking individuals (Mitchell et al., 2016), and during the second (Thoma et al., 2013), and third weeks (Maurage et al., 2011) of detoxification, but not during the early stages. Moreover, statistical methods that can support both the presence and absence of effects (e.g., Bayesian hypothesis testing; Quintana and Williams, 2008) have yet to be applied in this field. Thus, the aim of this study was to investigate whether intranasal oxytocin influenced social emotional recognition in patients during the first three days of acute alcohol detoxification using a combination of frequentist and Bayesian approaches.

2. Material and methods

2.1. Study design

The study was a part of a double blind, randomized placebo-controlled trial on intranasal oxytocin in alcohol withdrawal, including 39 patients admitted for alcohol detoxification at the Blue Cross Lade Addiction Treatment Centre (LBS) in Trondheim, Norway (Melby et al., 2019). The study was approved by the Regional Committee for Medical and Health Research in Central Norway (No. 2016/45) and the Norwegian Medicines Agency (No. 2015-004463-37) and was registered in clinicaltrials.gov (identifier NCT02903251). Eligible subjects were 18-65 years of age who lived in Trøndelag county, Norway. Further inclusion criteria are presented in detail elsewhere (Melby et al., 2019). To be included in the study, the average alcohol consumption was required to be in the range of 8-30 standard drinks (one standard drink = 12.8 g alcohol) per day for at least two weeks prior to enrolment in the study, which was assessed using the Timeline Follow-Back (TLFB) (Sobell et al., 1988).

2.2. Intranasal oxytocin Intervention

Patients were included in the study at the day of admission to the treatment centre. Written informed consent was obtained from all eligible patients fulfilling the inclusion criteria. If subjects were visibly intoxicated or experienced moderate withdrawal at admission, the informed consent procedure was repeated the following day. An assessment with Clinical Institute Withdrawal Assessment – Alcohol revised (CIWA-Ar) was performed immediately after admission. Pharmacological treatment following standard practice at the ward was given at CIWA-Ar scores of 10 or above (Melby et al., 2019), before commencing any further study procedures.

Oxytocin nasal spray (Syntocinon; Alfaisigma S.p.A., Bologna, Italy) and placebo were decanted into identical 10 ml pump-actuated nasal spray containers. The placebo spray contained identical constituents as the Syntocinon spray, except for the active ingredient. Randomization to oxytocin or placebo was performed using a web-based randomization system. Six nasal spray puffs were administered (containing a total dose of 24 IU oxytocin or placebo) in interchanging nostrils with 15-

second intervals twice daily for three days at 9 am and 6 pm. The use of nasal spray devices was based on the recommendations for standardization of the use of intranasal oxytocin in clinical trials (Guastella et al., 2013) and adapted to fit the routines at the ward. Study nurses monitored self-administration at the ward. The RMET was split into two parts reduce any practice effects. On day 2, patients completed the first 18 RMET items with test start approximately 40 minutes after nasal spray administration whereas the last 18 RMET items were completed approximately 40 minutes after nasal spray administration on day 3.

2.3. Main outcome measure

The Norwegian version of the thirty-six item RMET was used (Baron-Cohen et al., 2001). Stimuli were photographs of the human eye region presented on a black background in the center, surrounded by four labels with mental state descriptions in the corners. The patients were instructed to select the description they thought best matched what the person in the photograph was thinking or feeling. The primary endpoint was any difference in the number of correct answers

2.4. Statistical analysis

As this study was embedded in a randomized clinical trial on the effect of oxytocin on benzodiazepine use during alcohol withdrawal the power calculation was based on that endpoint (Melby et al., 2019). Statistical analyses were performed with R and JASP version 0.14.1 (2020). Patients, clinical personnel, researchers and statisticians were blinded to group allocation until the statistical calculations were finished.

Performance on the RMET on day 2 and day 3 between oxytocin and placebo groups were compared using Welch's t-test. To assess the relative evidence for an alternative and null hypothesis, we performed Bayesian hypothesis testing (Quintana and Williams, 2018). A Bayes factor value greater

than 3 was considered to be moderate evidence for one model relative to the other. An “Oosterwijk” informed prior distribution (a t-distribution centred at 0.35, with a scale of 0.102 and 3 degrees of freedom) was used, as this represents the small-to-medium effects typically observed in the biobehavioral sciences. In addition, we fitted a linear regression model with RMET performance as the outcome, and treatment group, oxazepam treatment doses during detoxification, alcohol intake, and the interaction of alcohol intake and treatment, as predictors. A Bayesian regression model with the same parameters was also fit with an r scale of 0.354 used for the prior distribution scale. A Bayes factor value greater than 3 was considered to be moderate relative evidence for models.

3. Results

Thirty-seven out of the 39 patients included in the main study (18 in the oxytocin and 19 in the placebo group) completed the RMET on day 2 and 3 (Supplementary Figure 1). Baseline characteristics are presented in Supplementary Table 1. On day 2, the difference of RMET performance was not statistically significant (a mean score of 11.56 in the oxytocin group vs. 10.95 in the placebo group; difference = 0.61, 95% CI [-0.63, 1.84], $t(35.70) = 0.99$, $p = 0.327$; Cohen's $d = 0.33$, 95% CI [-0.33, 0.99]; Figure 1A). Similarly, the difference of RMET performance on day 3 was not statistically significant (a mean score of 11.95 in the oxytocin group vs. 11.37 in the placebo group; difference = 0.58, 95% CI [-1.21, 2.37], $t(31.26) = 0.66$, $p = 0.514$; Cohen's $d = 0.24$, 95% CI [-0.47, 0.94]; Figure 1B). Bayesian t-tests revealed that there was 3.94 times more evidence for a null model relative to an alternative model for RMET differences at day 2 and 3.14 times more evidence for a null model relative to an alternative model for RMET differences at day 3 (Figure 1C and 1D). There was no significant difference in RMET scores when combining scores from day 2 and day 3 (a mean score of 23.61 in the oxytocin group vs. 22.16 in the placebo group; difference = -1.45, 95% CI [-4.24, 1.33], $t(33.01) = -1.06$, $p = 0.3$; Cohen's $d = -0.35$, 95% CI [-1, 0.3]. A Bayesian t-test revealed that there was 4.09 times more evidence

for a null model relative to an alternative model in combined RMET performance.

Diagnostic tests revealed sufficient quality for the model predicting RMET performance by treatment group, alcohol intake, and their interaction, for day 2 and day 3. The RMET day 2 model was statistically significant [$F(3,34) = 2.9, p = 0.049$], accounting for 13.3% of the variance in RMET performance. Alcohol use was a statistically significant predictor of RMET performance ($t = -2.2, p = 0.032$), however treatment group ($t = -0.84, p = 0.41$), or the treatment group x alcohol use interaction ($t = 0.4, p = 0.69$) coefficients were not statistically significant. The relationship between RMET performance on day 2 and alcohol use, grouped by treatment condition, is presented in Figure 2A. In terms of Bayesian linear regression, the full model ($BF_{01} = 1.93$), main effects model ($BF_{01} = 1.06$), and group only model ($BF_{01} = 2.40$) demonstrated anecdotal evidence for the null hypothesis. The alcohol only model demonstrated anecdotal evidence for the alternative model ($BF_{10} = 1.88$).

The RMET day 3 model was not statistically significant [$F(3,34) = 1.8, p = 0.16$], with the full model accounting for 6.3% of the variance in RMET performance. For the individual coefficients, alcohol use ($t = -1.74, p = 0.09$), treatment group ($t = -0.46, p = 0.65$), and the treatment group x alcohol use interaction ($t = 1.3, p = 0.9$) coefficients were not statistically significant. The relationship between RMET performance on day 3 and alcohol use, grouped by treatment condition, is presented in Figure 2B. In terms of Bayesian linear regression, the full model ($BF_{01} = 5.44$) demonstrated moderate evidence for the null hypothesis, relative to the alternative hypothesis. The main effects ($BF_{01} = 2.2$) and treatment group only ($BF_{10} = 2.71$) models demonstrated anecdotal evidence for the null hypothesis. The models assessing alcohol use demonstrated anecdotal evidence for the alternative model ($BF_{10} = 1.1$). There were no significant differences between the groups on day 2 and day 3 when adding oxazepam dosage as a covariate (data not shown).

4. Discussion

The main finding in this study was that oxytocin administration during alcohol withdrawal in alcohol-dependent patients did not improve social cognition performance. Moreover, alcohol use before detoxification significantly predicted RMET performance on day 2, but not on day 3 of withdrawal. Other studies have investigated RMET performance later in the detoxification process, such as day 8 of detoxification (Thoma et al., 2013), during the third week of detoxification (Maurage et al., 2011), after at least three weeks after detoxification (Nandrino et al., 2014) and after about six weeks of abstinence (Kopera et al., 2018). Three of these studies (Maurage et al., 2011; Nandrino et al., 2014; Thoma et al., 2013) showed that alcohol dependent patients had impaired social cognition with lower mean RMET scores than the healthy controls on the total score. Yet, no significant differences were seen in the study with 92 alcohol dependent patients and healthy controls (Kopera et al., 2018). The authors of the latter study suggest that gender, subgroups of alcohol dependent patients, or comorbid depression might explain the different outcomes between studies. Prior research of oxytocin in healthy subjects and patients with mental disorders has also shown conflicting results. For example, oxytocin has been reported to increase RMET scores in neurotypical men (Domes et al., 2007), yet these findings could not be replicated (Radke and de Bruijn, 2015). We did not investigate differences in early attachment and childhood trauma in the treatment groups, which might influence the effects of oxytocin (Mitchell et al., 2016).

The sample size in the present study and analysis was relatively small, which is due to the study being designed to detect other outcomes. However, the data were sensitive enough to yield a Bayes factor which provided moderate evidence for the null model relative to the alternative model. Also, dividing the RMET in two parts, with the first 18 items on day 2 and the last 18 on day 3, to keep the test load as low as possible during detoxification and to help prevent practice effects, may have influenced the operationalization of social cognition. Moreover, patients were receiving

benzodiazepines during study to alleviate withdrawal symptoms, and there is a potential risk that benzodiazepine intake may affect RMET scores. However, adding benzodiazepine intake as a covariate in the analyses did not affect the results. Altogether, our study provided moderate evidence that 2 or 3 days of oxytocin treatment during alcohol withdrawal does not influence RMET performance. Importantly, we used Bayesian hypothesis testing to specifically assess evidence for the null model, relative to the alternative, which is not possible using a conventional frequentist p -value approach.

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Figure 1. RMET scores in in patient with alcohol dependence undergoing treatment with oxytocin or placebo. Raincloud plots illustrate the number of correct answers on RMET performance on day 2 (A) and day 3 (B) during acute alcohol withdrawal in the oxytocin and placebo treatment groups. These show the data distribution (i.e., a split-half violin plot), the raw jittered data points, and a boxplot illustrating the median and interquartile range. Plots are also shown illustrating the prior and posterior distributions for the Bayesian independent samples t-test for RMET performance on day 2 (C) and day 3 (D).

Figure 2. The relationship between alcohol use and RMET performance in patients with alcohol dependence undergoing treatment. Data is shown for RMET performance during day 2 (A) and day 3 (B) of treatment with either oxytocin or placebo.