
Article

Efficacy of Self-Administered Intranasal Oxytocin on Alcohol Use and Craving After Detoxification in Patients With Alcohol Dependence. A Double-Blind Placebo-Controlled Trial

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Abstract

Aims: The aim of this study was to assess the efficacy of self-administered intranasal oxytocin on alcohol dependence after detoxification.

Methods: In a double-blind, randomized, placebo-controlled trial, 38 patients fulfilling the criteria for ICD-10 diagnosis of alcohol dependence received either 8 IU oxytocin or placebo at their own discretion up to thrice daily for 4 weeks, after completing detoxification. Primary outcome was alcohol intake specified as the amount of alcohol consumed, the number of days to relapse into alcohol use and the proportion of subjects relapsing. Secondary outcomes were self-reported symptoms of craving, sleep and mental distress.

Results: There were no significant differences between the oxytocin group and the placebo group in daily alcohol intake in total (mean 1.3 ± 2.9 vs. 2.0 ± 5.0 units; $P = 0.63$) or on drinking days (mean 8.4 ± 2.7 vs. 7.7 ± 6.0 units; $P = 0.76$), in the number of days until relapse ($P = 0.91$) or in the proportion of subjects relapsing (37.5 vs. 41.2%; $P = 0.84$). Neither were there any statistically significant differences in any other outcomes, except a larger decrease in self-reported nervousness in the oxytocin group ($P = 0.022$).

Conclusion: The results were inconclusive as to whether intranasal oxytocin reduced the time to relapse, degree of craving or total amount of alcohol consumed after detoxification. However, the oxytocin group had a larger decrease in self-reported nervousness.

INTRODUCTION

The short-term risk of relapse to alcohol use in patients with alcohol dependence after successful detoxification is high and is significantly associated with insomnia, anxiety, depression and cravings (Brower 2001). Several pharmacological agents aiming to reduce or prevent alcohol use in such patients by decreasing craving are available, such as baclofen, acamprosate, naltrexone and nalmefene. However, they have modest treatment effects (Palpacuer et al. 2018) and are not very often prescribed (Heldal et al. 2018). The lack of effective treatment underlines the need for an agent which is safe and easy to administer, with few adverse effects and no addictive potential.

The neuropeptide oxytocin is considered a part of the anti-stress system in the brain (Becker 2017; Bowen and Neumann 2017), and several studies in humans have indicated that oxytocin may facilitate social interaction and reduce anxiety (Neumann and Slattery 2016; Strathearn et al. 2019). In studies in animals, exogenously administered oxytocin has been effective in inhibiting self-administration of alcohol, including a long-lasting decline in the preference of alcoholic beverage relative to non-alcoholic sweet solutions. Oxytocin has also been shown to attenuate reinstatement of alcohol seeking to conditioned cues or stress in alcohol-dependent rats (for a review, see (King et al. 2020)).

A few studies have assessed the effects of oxytocin nasal spray on alcohol use and craving in humans (Mitchell et al. 2016; Hansson et al. 2018; Flanagan et al. 2019; Stauffer et al. 2019), using different measures and outcomes. In a functional magnetic resonance imaging study, potentially favorable oxytocin responses to cue-reactivity to alcohol in social drinkers were seen (Hansson et al. 2018). Oxytocin reduced craving in a subgroup with more anxiously attached, non-treatment-seeking individuals with alcohol abuse, but increased craving was seen in less anxiously attached individuals (Mitchell et al. 2016). Yet, oxytocin did not seem to affect alcohol craving, heart rate or cortisol levels in patients with alcohol use disorder and posttraumatic stress disorder (Flanagan et al. 2019; Stauffer et al. 2019). Despite these inconsistent findings, oxytocin is thought to be a potential treatment for alcohol dependence, although its neurobiological and behavioral effects are nuanced (Lee and Weerts 2016).

In this study, we hypothesized that self-administered intranasal oxytocin would have a positive effect on anxiety and craving, thereby reducing the risk of relapse and alcohol intake in patients with alcohol dependence the first four weeks after inpatient detoxification. The primary aim was to investigate the effect of oxytocin on alcohol consumption, measured as the amount of alcohol consumed, the number of days to relapse into alcohol use and the proportion of subjects relapsing. Secondary aims were to assess the effects of oxytocin on self-reported craving, sleep and mental distress, including anxiety/nervousness.

MATERIALS AND METHODS

Subjects

A total of 38 patients aged 18–65 years, fulfilling the criteria of ICD-10 diagnosis of alcohol dependence (F10.2), were included in the study. Eligible individuals were 18–65 years of age and lived in the county of Trøndelag, Norway. Further inclusion criteria were either a prior episode of withdrawal symptoms causing significant incapacitation (e.g. inability to work or perform every day activities) or at least one prior medical detoxification with withdrawal symptoms of a magnitude requiring sedative-hypnotic or anticonvulsant medication.

In addition, the average alcohol consumption should be in the range of 8–30 standard drinks per day for at least two weeks prior to detoxification. The exclusion criteria were as follows: daily treatment with sedative-hypnotic medications such as benzodiazepines or benzodiazepine-like hypnotics; dependence on substances other than alcohol, nicotine or caffeine; inadequately treated, unstable and/or compromising somatic or psychiatric conditions; a body mass index <17 kg/m² or a history of anorexia nervosa or bulimia in the past 2 years; pregnancy; parturition or breastfeeding in the past 6 months and the inability to read or understand Norwegian sufficiently well to complete the study questionnaires.

Nasal spray

Empty nasal spray bottles and pumps were acquired from Wirth Emballage, Åkersberga, Sweden. Oxytocin nasal spray (Syntocinon 4 IE per spray dose; Alfasiigma S.p.A., Bologna, Italy) and placebo were decanted into identical 10-ml nasal spray containers by Sanivo Pharma, Oslo, Norway. The placebo spray, which was also produced by Sanivo Pharma, contained identical constituents as the Syntocinon spray, except for the active ingredient oxytocin.

Study design

The study was designed as a two-part randomized double-blind, placebo-controlled trial. The first part of the study (hereafter referred to as Part 1) was a 3-day trial of oxytocin on alcohol withdrawal symptoms during acute inpatient detoxification. The results of this part have been published previously (Melby et al. 2019). The second part of the study (hereafter referred to as Part 2), which is presented here, was a 25-day extension study, aiming to evaluate the effect of oxytocin on alcohol intake, withdrawal symptoms and craving during the 4 weeks from inclusion.

The protocol for this research project has been approved by Regional Committee for Medical and Health Research in Central Norway (REK Midt) (No. 2016/45) and the Norwegian Medicines Agency (SLV) (No. 2015-004463-37) and registered in clinicaltrials.gov (identifier NCT02903251). The protocol conforms to the provisions of the Declaration of Helsinki. Informed consent was obtained from all the participants. The study was also approved and supported by the local User Committee at the treatment centre.

The power calculation was based on expected results of Part 1 of the trial, where detection of a difference of 10 mg in oxazepam consumption between groups during detoxification of alcohol was considered to be of clinical interest. Given an expected standard deviation of approximately 10 mg, power = 0.80 and alpha = 0.05, 16 participants in each group were needed (Melby et al. 2019). To account for dropouts, a total of 40 patients were included in the study, and 38 of these participated in Part 2 (Fig. 1).

Part 1 of the study started on the day of admittance to the clinic. The participants followed an inpatient withdrawal treatment schedule where study nurses administered six insufflations of nasal spray in alternating nostrils and 15 seconds apart, twice daily (in total 48 IU oxytocin daily in the oxytocin group) for 3 days (Melby et al. 2019). Before commencing Part 2, the participants were instructed in self-administration of the nasal spray and to use it as needed, i.e. when they experienced craving, with two insufflations (in total 8 IU), one in each nostril and 15 seconds apart, up to thrice daily (i.e. a maximum of 24 IU oxytocin daily in the oxytocin group, with no restrictions related to the time interval between the three dosages) for 25 days. Dosage as needed was chosen to reduce the number of dropouts,

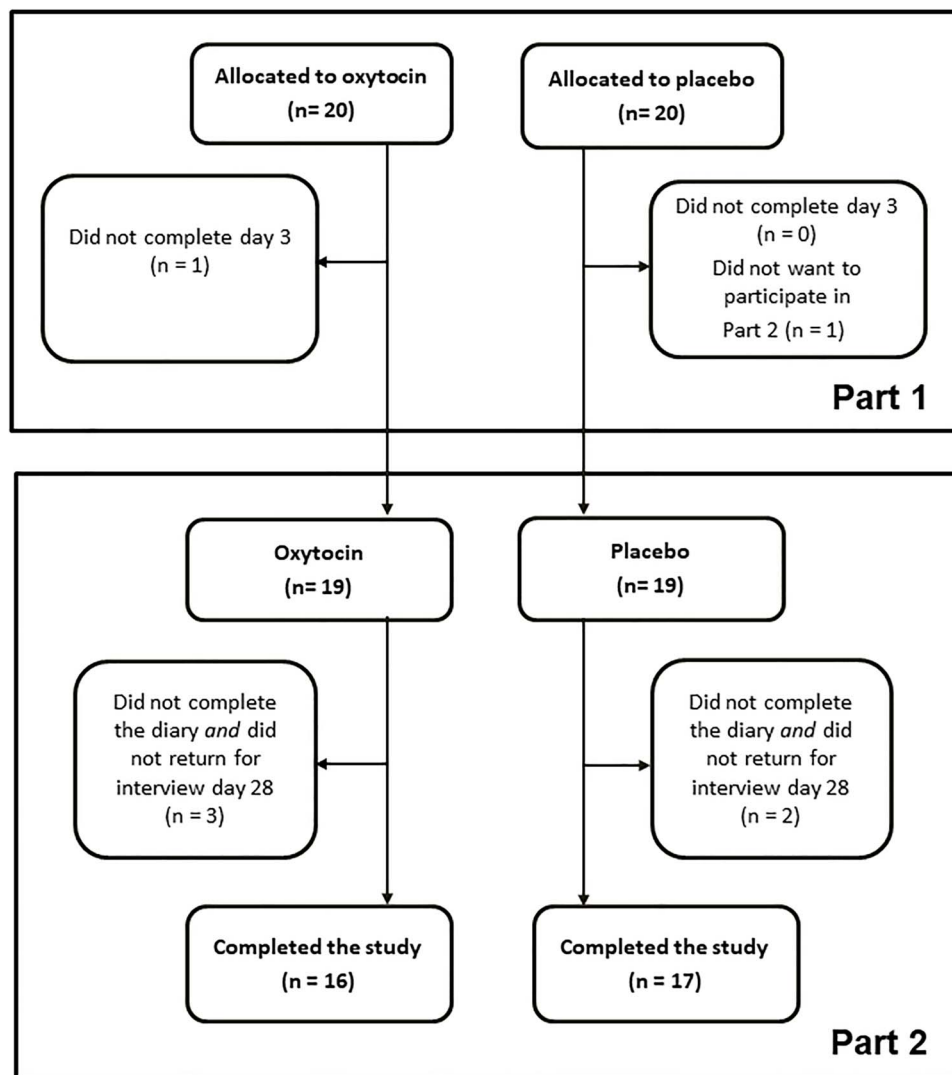


Fig. 1. Flow chart of the inclusion of patients and completion of the study according to the Consolidating Standard of Reporting Trials (CONSORT). Part 1 lasted 3 days and Part 2 lasted 25 days. The two subjects who did not complete Part 1 were not included in the study, as the registration of outcome data first started from Day 3.

as high dropout rates are a well-known phenomenon in this patient group (Prisciandaro et al. 2011). Moreover, because oxytocin has a rapid onset of action (with effects expected to peak at 20–60 minutes after intranasal administration) and is relatively short-acting (elevated oxytocin concentrations have been seen for 2–2.5 hours after administration), symptom-based treatment was considered a logical approach (Guastella et al. 2013). In most previous studies on craving in substance use disorders (alcohol as well as illicit drugs), doses have varied from 24 to 40 IU (Lee et al. 2014; Miller et al. 2016; Mitchell et al. 2016). Finally, long-term effects of intranasal oxytocin have not been investigated in this patient group previously (MacDonald et al. 2011). As the patients in our study should take the dose as needed for 4 weeks, we considered that giving a relatively low dose would be sufficient. The participants were given a diary and were instructed to log their use of nasal spray and alcohol daily during the study period.

Alcohol intake was assessed by a Timeline Followback (TLFB) interview at the final visit and end of the study. TLFB is a validated and frequently used method that helps patients to recall and quantify their alcohol intake (Sobell et al. 1988). In addition, a blood sample

for the analysis of alcohol marker phosphatidylethanol (PEth) was drawn at Day 3. PEth was repeated at the final visit, and self-reported alcohol use was derived from the patient diary.

Two questionnaires were filled in at the final visit. The Hopkins Symptom Check-List-10 (HSCL-10) is a 10-item questionnaire used to assess psychiatric symptoms of anxiety and depression, and is a short version of the HSCL (Derogatis et al. 1974). Values above 1.85 have been found to indicate appearance of anxiety and/or depression in an alcohol-dependent population (Strand et al. 2003). The Alcohol Craving Questionnaire-Short Form-Revised (ACQ-SF-R) is a 12-item questionnaire derived from the 47-item Alcohol Craving Questionnaire, which assesses craving for alcohol among alcohol users at the time the questionnaire is answered. The scoring scale ranges from 1 (strongly disagree) to 7 (strongly agree). ACQ-SF-R has four subscales: compulsivity, expectancy, purposefulness and emotionality. Patients with high scores have been found to report higher urges to drink in anticipation of relief from withdrawal or negative affect compared to individuals with low scores (Martin et al. 2003).

Table 1. Baseline characteristics and clinical data at inclusion of 38 patients undergoing alcohol detoxification and treated with either oxytocin nasal spray or placebo

	Oxytocin group (n = 19)	Placebo group (n = 19)	P value*
Gender (males/females)	12/7	15/4	0.28
Age (years), mean \pm SD	48.4 \pm 11.4	46.4 \pm 9.8	0.56
Marital status (single/cohabiting)	13/6	13/6	1.00
Employed (yes/no)	5/14	4/15	0.70
Self-reported daily alcohol intake during the last 14 days before inclusion (standard alcohol units**), mean \pm SD	16.1 \pm 7.2	15.3 \pm 6.4	0.72
Phosphatidylethanol blood concentration at inclusion (μ mol/L), mean \pm SD	2.24 \pm 1.15	2.13 \pm 1.21	0.78
HSCL-10, mean \pm SD***	2.51 \pm 0.56	2.57 \pm 0.72	0.78
ACQ-SF-R, mean \pm SD***	3.27 \pm 1.03	3.06 \pm 1.58	0.63

SD = standard deviation.

*Independent samples *t*-test or chi-square test as appropriate.

**One standard alcohol unit corresponds to 12.8 g ethanol.

***Score at Day 3 of detoxification.

Other variables obtained from the diary were the degree of alcohol craving, the number of awakenings and sleeping hours every night, symptoms related to mental distress (nervousness and sociability), and any relief and possible adverse events associated with the nasal spray. These variables were rated from 0 (none) to 6 (severe) on a Likert scale on a daily basis. Sleep quality was rated from 1 (very well) to 5 (very poor).

At the end of the study, patients returned the nasal spray bottles and diary to the study nurses. The nasal spray bottles were weighed before use and at the final check-up to estimate the number of doses used. Three attempts were made by phone to contact patients who did not show up at the check-up. All available data from diaries, the check-up, interviews and telephone calls were combined to create the data file.

Statistical analyses

Results are presented as means \pm standard deviations (SDs) with 95% confidence intervals (CIs) as appropriate. The level of significance was set to $P = 0.05$. Statistical analyses were performed with IBM SPSS Statistics for Windows, version 25.0. Independent samples *t*-tests and chi-square tests were used to assess the differences between groups. Kaplan–Meier estimates of cumulative proportions and log-rank tests were applied to compare the time to relapse between the two groups. Self-reported alcohol intake during the study period and/or a positive PEth analysis at the end of the study were defined as relapse. Non-completion of the study period was not considered as relapse, but patients were treated as censored from the time of dropout, based on recommendations for statistical analyses in alcohol research (Hallgren and Witkiewitz 2013). A linear mixed model was used to estimate changes over time and difference between groups in the diary data during the 28 days of study. Distributional assumptions were checked by visual inspection of histograms and residual plots. If potentially violated, sensitivity analyses using the Wilcoxon–Mann–Whitney test were also performed to assess the robustness of the findings.

RESULTS

In total, 22 of the 38 patients (12 in the oxytocin group and 10 in the placebo group) completed the diary for the whole study period

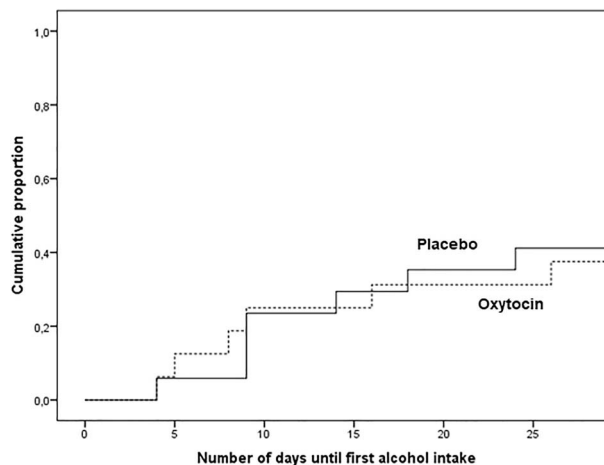


Fig. 2. Number of days until first alcohol intake in the oxytocin ($n = 16$) and the placebo ($n = 17$) groups, presented as cumulative proportion in a Kaplan–Meier survival plot. There was no difference between the treatment groups ($P = 0.91$).

of 28 days. A total of 28 patients (13 in the oxytocin group and 15 in the placebo group) attended the check-up at Day 28. Thus, taken together, 33 of the 38 patients, i.e. 87% (16 in the oxytocin group and 17 in the placebo group) completed their diary and/or attended the check-up (Fig. 1). Baseline characteristics of the patients and clinical data at inclusion are presented in Table 1.

There were no differences between the groups in the proportion of patients relapsing during the study period (6 of 16; 37.5% in the oxytocin group vs. 7 of 17; 41.2% in the placebo group; $P = 0.84$), or in time to relapse ($P = 0.91$) (Fig. 2). If all dropouts were counted as relapses in addition to those who were known relapses, the proportion of relapses would be 10 of 16 (62.5%) in the oxytocin group and 11 of 17 (64.7%) in the placebo group ($P = 0.74$).

We also checked time to relapse in subgroups related to the degree of alcohol consumption before inclusion. Neither in patients with a mean daily alcohol intake of >16 units the 14 days prior to inclusion (16 patients in total) nor in patients with a mean alcohol intake of ≤ 16 units (24 patients in total) were there any significant differences in time to relapse between oxytocin and placebo ($P = 0.75$ and

Table 2. Key outcome data of 38 patients 28 days after acute alcohol detoxification treated with either oxytocin nasal spray ($n = 19$) or placebo ($n = 19$)

	Oxytocin group Mean \pm SD	Placebo group Mean \pm SD	<i>P</i> value*	Difference (95% CI)
Alcohol units ^{**,***}	1.3 \pm 2.9	2.0 \pm 5.0	0.63	-0.7 (-3.6, 2.2)
Alcohol units on drinking days ^{**,†}	8.4 \pm 2.7	7.7 \pm 6.0	0.76	0.7 (-4.3, 5.8)
HSCL-10 score, total ^{††}	1.72 \pm 0.61	1.97 \pm 0.81	0.39	-0.25 (-0.81, 0.33)
HSCL-10 score, anxiety	1.63 \pm 0.67	1.80 \pm 0.93	0.59	-0.17 (-0.81, 0.47)
HSCL-10 score, depression	2.67 \pm 0.95	3.11 \pm 1.23	0.33	-0.42 (-1.34, 0.47)
Change in total HSCL-10 score ^x	-0.81 \pm 0.68	-0.57 \pm 0.60	0.35	-0.24 (-0.75, 0.27)
ACQ-SF-R score, total ^{†††}	2.59 \pm 0.96	2.81 \pm 1.53	0.67	-0.22 (-1.25, 0.82)
ACQ-SF-R score, compulsivity	1.62 \pm 0.89	1.93 \pm 1.19	0.45	-0.31 (-1.15, 0.53)
ACQ-SF-R score, expectancy	2.74 \pm 1.34	2.93 \pm 1.61	0.75	-0.18 (-1.36, 0.99)
ACQ-SF-R score, purposefulness	3.13 \pm 1.70	2.64 \pm 1.69	0.47	0.49 (-0.88, 1.86)
ACQ-SF-R score, emotionality	2.87 \pm 1.90	3.55 \pm 2.05	0.38	-0.68 (-2.25, 0.90)
Change in total ACQ-SF-R score ^x	-0.42 \pm 1.26	-0.21 \pm 1.08	0.65	-0.21 (-1.16, 0.74)
Phosphatidylethanol blood concentration (μ mol/L)	0.46 \pm 0.59	0.55 \pm 1.01	0.78	-0.09 (-0.75, 0.57)

CI = confidence interval; SD = standard deviation.

*Independent samples *t*-test.

**One standard alcohol unit corresponds to 12.8-g ethanol.

***Mean daily number of alcohol units consumed on all days.

†Mean number of alcohol units consumed on days with alcohol intake.

††Hopkins Symptom Check List-10.

†††Alcohol Craving Questionnaire-Short Form-Revised.

^xChange in score from baseline to Day 28.

$P = 0.99$, respectively; Kaplan–Meier survival analyses). Similarly, there were no significant differences between treatment groups in those with a PEth blood concentration $>2 \mu\text{mol/l}$ (20 patients in total; $P = 0.74$) or in those with a concentration $\leq 2 \mu\text{mol/l}$ (20 patients in total; $P = 0.56$). Separate analyses in those with HSCL-10 scores ≥ 2 (31 patients in total) and in those with ACQ-SF-R scores ≥ 3 (23 patients in total) did not reveal any significant differences in symptoms of anxiety/depression or craving between oxytocin and placebo ($P = 0.33$ and $P = 0.18$, respectively). Because of the small sample size, no further subgroup analyses were performed.

The mean daily alcohol intake in the whole period, the mean daily alcohol intake on drinking days and the PEth blood concentration at Day 28 did not differ between groups (Table 2). Neither were there any differences in HSCL-10 or ACQ-SF-R scores at Day 28 or in the changes in HSCL-10 or ACQ-SF-R scores from baseline to Day 28 between the oxytocin and the placebo groups (Table 2). However, there was a significant decrease in HSCL-10 score from baseline to Day 28 both within the oxytocin group (from 2.53 ± 0.65 to 1.72 ± 0.61 in the 13 patients with complete data; $P = 0.001$) and within the placebo group (from 2.54 ± 0.81 to 1.96 ± 0.81 in the 14 patients with complete data; $P = 0.004$). No significant decreases from baseline to Day 28 were found in ACQ-SF-R scores within these two groups ($P = 0.25$ and $P = 0.49$, respectively).

The mean daily number of oxytocin spray doses used was 3.11 in the oxytocin group and 4.37 in the placebo group, out of a maximum number of six. When restricting data to patients who had used a mean of ≥ 3 spray doses per day (i.e. at least 75 spray doses throughout the 25-day Part 2 study period), there was no difference in the number of alcohol units consumed on drinking days (oxytocin $n = 6$, 7.9 ± 2.5 units vs. placebo $n = 7$, 7.0 ± 4.8 units, difference 0.9 units, CI -3.9 to 5.7 units, $P = 0.68$).

There were no differences between the groups in the degree of alcohol craving, sleep, sociability or subjective relief after using the spray during the 28 days (Table 3). However, self-reported

nervousness decreased more significantly over time in the oxytocin group than in the placebo group ($P = 0.022$). There were no differences in the number of self-reported adverse effects between the groups (Table 3); the volume of nasal spray at each dosing was the most frequent complaint in both groups.

DISCUSSION

In this study, no significant differences were observed between the oxytocin group and the placebo group in the number of days until relapse, the proportion of patients with relapse during the study or the total amount of alcohol ingested during the 28-day treatment period. Neither were there any significant differences between the two treatment groups in self-reported craving, sleep, anxiety, relief by nasal spray or sociability.

The use of intranasal oxytocin in clinical trials in addiction is yet in an early phase, and there are only a handful studies on alcohol use disorders and dependence. As reported in our 3-day study on acute alcohol withdrawal, no clear-cut effects of intranasal oxytocin were seen (Melby et al. 2019), in contrast to the results from a small pilot study (Pedersen et al. 2013). The few previous studies assessing the effects of oxytocin nasal spray on alcohol craving (Pedersen et al. 2013; Mitchell et al. 2016; Hansson et al. 2018; Flanagan et al. 2019; Melby et al. 2019; Stauffer et al. 2019) have not found any positive effects on craving in general, although one study reported an effect in a subgroup with more anxiously attached subjects (Mitchell et al. 2016). The long-term effects of oxytocin in patients with alcohol dependence are not known, but oxytocin has been suggested to reduce tolerance to alcohol in rodents and in humans (Lee and Weerts 2016; King et al. 2020). These studies are mainly pilot studies with a few participants, with different populations and outcome measures.

Similar to studies on alcohol, the effects of exogenously administered oxytocin on craving and relapse in patients with substance

Table 3. Estimates of sleep pattern, alcohol craving, nervousness, sociability and use of and effects of nasal spray in 38 patients after acute alcohol detoxification. The estimates are based on a linear mixed model of 4-week diary data and the patients were treated with either oxytocin nasal spray ($n = 19$) or placebo ($n = 19$). Statistically significant P values are shown in bold.

	Oxytocin group		Placebo group		P value [†]
	Mean	95% CI	Mean	95% CI	
Hours of sleep per night	6.92	6.27, 7.57	7.16	6.54, 7.79	0.97
Number of awakenings per night	1.53	0.75, 2.31	1.80	1.04, 2.56	0.33
Sleep quality [‡]	2.20	1.84, 2.55	2.31	1.95, 2.66	0.90
Alcohol craving [§]	1.00	0.44, 1.57	1.49	0.94, 2.04	0.94
Nervousness [§]	1.37	0.66, 2.09	2.22	1.52, 2.92	0.022
Sociability [§]	2.03	1.34, 2.73	1.94	1.31, 2.57	0.99
Relief of nasal spray [§]	2.67	1.93, 4.42	1.90	1.23, 2.57	0.74
Adverse effects [§]	0.11	-0.28, 0.51	0.68	0.32, 1.04	0.99

CI = confidence interval.

[†]Linear mixed model.

[‡]Likert scale: 1 (very well) to 5 (very poor).

[§]Likert scale: 0 (none) to 5 (severe).

use disorders seem to be complex. In cocaine-dependent individuals, an increase in craving was seen (Lee et al. 2014). Peculiarly, in cocaine users with concomitant opioid dependence, oxytocin seemed to decrease craving of cocaine, but not heroin (Stauffer et al. 2016). No effects of oxytocin on opioid craving were seen in a pilot study in heroin-dependent patients (Woolley et al. 2016), but in another study, oxytocin reduced opioid craving (Moeini et al. 2019). Oxytocin has also been found to reduce self-reported cannabis use (Sherman et al. 2017) and to decrease cannabis craving (McRae-Clark et al. 2013). In two recent studies in cigarette smokers, no effect of oxytocin on nicotine craving was found (McClure et al. 2020; Van Hedger et al. 2020). Also similar to studies on alcohol dependence, these studies are mostly pilot studies on different substances, on subjects in different stages of dependence, with small sample sizes and with methodological diversities related to both design and outcomes.

Craving is an important subjective clinical symptom, but it is difficult to measure as it is associated with control, urge or desire, anticipation of effects and intent to use (Koob and Volkow 2016). In fact, patients in both treatment groups reported no or mild craving, both according to the ACQ-SF-R and the diary recordings. Nevertheless, a significant proportion of subjects in both groups (37.5% in the oxytocin group and 41.2% in the placebo group) relapsed during the treatment period. This might reflect a lack of treatment effect of oxytocin or, alternatively, that craving in both patient groups was already low or that the methods of assessing craving were insufficient.

About 10% of a general population in Norway were found to have HSCL-10 scores above cut-off value of 1.85 (Strand et al. 2003). In this study, the mean HSCL-10 scores in both treatment groups at Day 28 were around the cut-off value of 1.85, indicating that patients had symptoms of anxiety and depression. This supports earlier findings on the occurrence of anxiety and depression in patients with alcohol dependence (Wetterling and Junghanns 2000; Hoxmark et al. 2010). The reduction in HSCL-10 scores from Day 3 to Day 28 is also consistent with what is seen in the previous studies (Wetterling and Junghanns 2000; Hoxmark et al. 2010).

A statistically significant difference in self-reported nervousness was seen between the groups during the 28 days of treatment. Nervousness, uneasiness and anxiety are terms used to rate self-perceived anxiety. The relationship between anxiety and alcohol is complex, but the reduced nervousness in the oxytocin group did not cause a

significantly reduced alcohol intake in this group. Moreover, as we did not find any such differences on the anxiety subscale of HSCL-10, we cannot exclude that the effect on self-reported nervousness is a coincidence. In a study in non-treatment-seeking patients with alcohol use disorder, oxytocin nasal spray enhanced social perception in those with a history of attachment anxiety (Mitchell et al. 2016). We did not find any effect of oxytocin on sociability in the present study. Furthermore, in the same study (Mitchell et al. 2016), the effects of oxytocin seemed to be moderated by the attachment style, as less anxiously attached patients reported increased and not decreased craving after oxytocin administration.

This study has several limitations that should be mentioned. The pragmatic approach of administering the nasal spray as needed, instead of a fixed daily dose, was chosen based on an assumption that more patients would be able to complete the trial. In clinical trials in patients with alcohol dependence who also had bipolar disorder, dropout rates of 40 to 74% have been reported (Prisciandaro et al. 2011). A relationship between alcohol abuse and the risk of dropping out during treatment for alcohol dependence was seen in five out of 26 studies in a systematic review assessing risk factors of dropout from addiction treatment (Brorson et al. 2013).

High dropout rates increase the risk of bias when estimating treatment effects in alcohol trials, particularly when all dropouts are counted as relapses (Hallgren and Witkiewitz 2013). Thus, as such, the approach of letting the patients use the spray at their own discretion (within certain limits) could be one factor contributing to the relatively low dropout rate of 13% in our study. However, this study design also made some of the outcomes possibly based on effects of oxytocin more difficult to discern. As the patients were instructed to use the spray when they experienced craving, there is an obvious risk that we would be unable to find any positive effect of intranasal oxytocin on craving due to more spray use on days with more pronounced craving. Another explanation could be that the level of craving was already low in both patient groups, and that we therefore were not able to discern any differences. We had the intention to compensate for these uncertainties by asking the patients to note the number of sprays used every day in the diary. Unfortunately, the information on the daily number of sprays found in the diary turned out to be unreliable, as the number of doses reported to have been used was not consistent with the total number

of doses missing when weighing the spray bottles at the end of the study. In theory, one explanation why the oxytocin group used less nasal spray than the placebo group could be that they experienced less craving due to a treatment effect. However, based on the results from our previous studies as well as from this study, we consider this explanation to be unlikely (Melby et al. 2019; Melby et al. 2020).

In most previous studies on craving in substance use disorders (alcohol as well as illicit drugs), doses have been varied from 24 to 40 IU (Pedersen et al. 2013; Lee et al. 2014; Mitchell et al. 2015; Miller et al. 2016; Melby et al. 2019). Our patients were given the opportunity to use nasal spray as needed, 8 IU per dose, until a maximum daily dose of 24 IU. Thus, the amount of nasal spray could potentially be below a lowest effective dosage. The only commercially available spray provided 4 IU oxytocin per spray dose of 0.1 ml. Thus, although using both nostrils, there is an obvious risk that administering 40 IU, i.e. five spray doses or 0.5 ml per nostril, would cause nasal overflow with an unknown amount of fluid being transported to the mouth and swallowed, with consequent inactivation of oxytocin in the gastrointestinal tract. In contrast, a volume of one spray dose (0.1 ml) in each nostril was clearly acceptable without any risk of gastrointestinal inactivation. It should also be noted that there are data showing that a lowest effective dosage at least for some effects could be considerably lower than 40 IU. For example, one study found that a single dose of 8 IU, but not 24 IU, had a significant effect on emotional salience, pupil diameter and right amygdala activation (Quintana et al. 2017).

Another limitation of this study is the small sample size. The sample size estimation was based on the primary outcome in Part 1 of this trial. A few patients lost to follow-up during Part 2, resulted in an even smaller sample size with correspondingly wide CIs, particularly for some of the outcomes. Thus, the non-significant results in this study cannot be interpreted as conclusive evidence that no differences exist between the groups. We did not investigate whether patients who relapsed noticed any change in their sensitivity to alcohol.

Since several secondary outcomes were compared between groups, the statistically significant change in nervousness could be a chance finding due to multiple testing, although it makes sense from a pharmacological point of view (Neumann and Slattery 2016; Strathearn et al. 2019). It should also be noted that some potentially interesting baseline characteristics, such as the patients' attachment at young age and the number of years of alcohol abuse, have not been taken into consideration. Finally, no genetic testing was performed to investigate whether some oxytocin receptor gene variants could be associated with the effects of intranasal oxytocin. We did not investigate whether patients who relapsed noticed any change in their sensitivity to alcohol.

There is an ongoing discussion related to the uptake of oxytocin from the nasal cavity and its transport to the brain when used as a nasal spray. Anatomical variations in the nasal cavity have been shown to affect the bioavailability and uptake of oxytocin in plasma (Quintana et al. 2017). Also, the uptake mechanism to the brain is not fully understood. As oxytocin does not cross the blood-brain barrier, it most likely follows the olfactory nerve into the central nervous system.

One of the strengths of this trial is the methodology used, being double-blind, randomized and placebo-controlled. The clinical approach, implementing the study into the already existing routines at the treatment center, meant that all study personnel were familiar with the study protocol, thereby probably also preventing a higher dropout rate. The protracted withdrawal symptoms and craving patients undergo in the post-detoxification period were clearly seen

in this study and underline the need for a better pharmacological treatment to prevent relapse.

In conclusion, in this study intranasal oxytocin was not found to affect the time to relapse, the proportion of patients relapsing, the total amount of alcohol ingested or the degree of alcohol craving, during the first four weeks after acute alcohol detoxification. There was, however, a decrease in self-reported nervousness in the oxytocin group. Further studies with a larger sample size, extended observation times and possibly also with regular and more frequent drug administration are warranted to assess whether oxytocin can be helpful in protracted alcohol withdrawal.

AUTHORS' CONTRIBUTIONS

The authors have contributed to the paper as follows: Design and protocol: K.M., R.W.G., T.A. and O.S. Obtaining of data: K.M. Calculations and analyses: E.S., K.M. and O.S. Preparation of the manuscript: K.M., R.W.G., T.A. and O.S., with input from E.S. All authors have approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

All relevant individual data are available by contacting the first author, mailto: katrine.melby@stolav.no.

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CONFLICT OF INTEREST STATEMENT

No conflict of interest.

REFERENCES

- Becker HC (2017) Influence of stress associated with chronic alcohol exposure on drinking. *Neuropharmacology* 122:115–26.
- Bowen MT, Neumann ID (2017) Rebalancing the addicted brain: oxytocin interference with the neural substrates of addiction. *Trends Neurosci* 40:691–708.

- Brorson HH, Ajo Arnevik E, Rand-Hendriksen K *et al.* (2013) Drop-out from addiction treatment: a systematic review of risk factors. *Clin Psychol Rev* 33:1010–24.
- Brower KJ (2001) Alcohol's effects on sleep in alcoholics. *Alcohol Res Health* 25:110–25.
- Derogatis LR, Lipman RS, Rickels K *et al.* (1974) The Hopkins symptom checklist (HSCL): a self-report symptom inventory. *Behav Sci* 19:1–15.
- Flanagan JC, Allan NP, Calhoun CD *et al.* (2019) Effects of oxytocin on stress reactivity and craving in veterans with co-occurring PTSD and alcohol use disorder. *Exp Clin Psychopharmacol* 27:45–54.
- Guastella AJ, Hickie IB, McGuinness MM *et al.* (2013) Recommendations for the standardisation of oxytocin nasal administration and guidelines for its reporting in human research. *Psychoneuroendocrinology* 38:612–25.
- Hallgren KA, Witkiewitz K (2013) Missing data in alcohol clinical trials: a comparison of methods. *Alcohol Clin Exp Res* 37:2152–60.
- Hansson AC, Koopmann A, Uhrig S *et al.* (2018) Oxytocin reduces alcohol cue-reactivity in alcohol-dependent rats and humans. *Neuropsychopharmacology* 43:1235–46.
- Heldal AT, Skurtveit S, Lobmaier PPK *et al.* (2018) Use of drugs for alcohol use disorder in Norway 2004–16. *Tidsskr Nor Laegeforen* 138. Norwegian.
- Hoxmark E, Benum V, Friborg O *et al.* (2010) Reduction in mental distress among substance users receiving inpatient treatment. *Int J Ment Health Syst* 4:30.
- King CE, Gano A, Becker HC (2020) The role of oxytocin in alcohol and drug abuse. *Brain Res* 1736:146761.
- Koob GF, Volkow ND (2016) Neurobiology of addiction: a neurocircuitry analysis. *Lancet Psychiatry* 3:760–73.
- Lee MR, Glassman M, King-Casas B *et al.* (2014) Complexity of oxytocin effects in a chronic cocaine dependent population. *Eur Neuropsychopharmacol* 24:1483–91.
- Lee MR, Weerts EM (2016) Oxytocin for the treatment of drug and alcohol use disorders. *Behav Pharmacol* 27:640–8.
- MacDonald E, Dadds MR, Brennan JL *et al.* (2011) A review of safety, side-effects and subjective reactions to intranasal oxytocin in human research. *Psychoneuroendocrinology* 36:1114–26.
- Martin PR, Singleton CK, Hiller-Sturmhofel S (2003) The role of thiamine deficiency in alcoholic brain disease. *Alcohol Res Health* 27:134–42.
- McClure EA, Baker NL, Gray KM *et al.* (2020) The influence of gender and oxytocin on stress reactivity, cigarette craving, and smoking in a randomized, placebo-controlled laboratory relapse paradigm. *Psychopharmacology (Berl)* 237:543–55.
- McRae-Clark AL, Baker NL, Maria MM *et al.* (2013) Effect of oxytocin on craving and stress response in marijuana-dependent individuals: a pilot study. *Psychopharmacology (Berl)* 228:623–31.
- Melby K, Fasmer OB, Henriksen TE *et al.* (2020) Actigraphy assessment of motor activity and sleep in patients with alcohol withdrawal syndrome and the effects of intranasal oxytocin. *PLoS One* 15:e0228700–e00.
- Melby K, Grawe RW, Aamo TO *et al.* (2019) Effect of intranasal oxytocin on alcohol withdrawal syndrome: a randomized placebo-controlled double-blind clinical trial. *Drug Alcohol Depend* 197:95–101.
- Miller MA, Bershada A, King AC *et al.* (2016) Intranasal oxytocin dampens cue-elicited cigarette craving in daily smokers: a pilot study. *Behav Pharmacol* 27:697–703.
- Mitchell IJ, Gillespie SM, Abu-Akel A (2015) Similar effects of intranasal oxytocin administration and acute alcohol consumption on socio-cognitions, emotions and behaviour: Implications for the mechanisms of action. *Neurosci Biobehav Rev* 55:98–106.
- Mitchell JM, Arcuni PA, Weinstein D *et al.* (2016) Intranasal oxytocin selectively modulates social perception, craving, and approach behavior in subjects with alcohol use disorder. *J Addict Med* 10:182–9.
- Moeini M, Omid A, Sehat M *et al.* (2019) The effects of oxytocin on withdrawal, craving and stress response in heroin-dependent patients: a randomized, double-blind clinical trial. *Eur Addict Res* 25:41–7.
- Neumann ID, Slattery DA (2016) Oxytocin in general anxiety and social fear: a translational approach. *Biol Psychiatry* 79:213–21.
- Palpacuer C, Duprez R, Huneau A *et al.* (2018) Pharmacologically controlled drinking in the treatment of alcohol dependence or alcohol use disorders: a systematic review with direct and network meta-analyses on nalmefene, naltrexone, acamprosate, baclofen and topiramate. *Addiction* 113:220–37.
- Pedersen CA, Smedley KL, Leserman J *et al.* (2013) Intranasal oxytocin blocks alcohol withdrawal in human subjects. *Alcohol Clin Exp Res* 37:484–9.
- Prisciandaro JJ, Rembold J, Brown DG *et al.* (2011) Predictors of clinical trial dropout in individuals with co-occurring bipolar disorder and alcohol dependence. *Drug Alcohol Depend* 118:493–6.
- Quintana DS, Westlye LT, Hope S *et al.* (2017) Dose-dependent social-cognitive effects of intranasal oxytocin delivered with novel breath powered device in adults with autism spectrum disorder: A randomized placebo-controlled double-blind crossover trial. *Transl Psychiatry* 7:e1136.
- Sherman BJ, Baker NL, McRae-Clark AL (2017) Effect of oxytocin pre-treatment on cannabis outcomes in a brief motivational intervention. *Psychiatry Res* 249:318–20.
- Sobell LC, Sobell MB, Leo GI *et al.* (1988) Reliability of a timeline method: assessing normal drinkers' reports of recent drinking and a comparative evaluation across several populations. *Br J Addict* 83:393–402.
- Stauffer CS, Meinerz NK, Morrison T *et al.* (2019) Effects of oxytocin administration on cue-induced craving in co-occurring alcohol use disorder and PTSD: a within-participant randomized clinical trial. *Alcohol Clin Exp Res* 43:2627–36.
- Stauffer CS, Musinipally V, Suen A *et al.* (2016) A two-week pilot study of intranasal oxytocin for cocaine-dependent individuals receiving methadone maintenance treatment for opioid use disorder. *Addict Res Theory* 24:490–8.
- Strand BH, Dalgard OS, Tambs K *et al.* (2003) Measuring the mental health status of the Norwegian population: a comparison of the instruments SCL-25, SCL-10, SCL-5 and MHI-5 (SF-36). *Nord J Psychiatry* 57:113–8.
- Strathearn L, Mertens CE, Mayes L *et al.* (2019) Pathways relating the neurobiology of attachment to drug addiction. *Front Psych* 10:737.
- Van Hedger K, Bershada AK, Lee R *et al.* (2020) Effects of intranasal oxytocin on stress-induced cigarette craving in daily smokers. *Nicotine Tob Res* 22:89–95.
- Wetterling T, Junghanns K (2000) Psychopathology of alcoholics during withdrawal and early abstinence. *Eur Psychiatry* 15:483–8.
- Woolley JD, Arcuni PA, Stauffer CS *et al.* (2016) The effects of intranasal oxytocin in opioid-dependent individuals and healthy control subjects: a pilot study. *Psychopharmacology (Berl)* 233:2571–80.