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Effect of intranasal oxytocin on alcohol withdrawal syndrome: A randomized placebo-controlled double-blind clinical trial

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ABSTRACT

Background: In a pilot study, intranasal oxytocin was demonstrated to reduce the benzodiazepine dose needed to relieve withdrawal symptoms during alcohol detoxification. The aim of the present study was to compare the effect of oxytocin and placebo during a three-day period of alcohol detoxification at an addiction treatment center in Norway.

Methods: Randomized, double-blind, placebo-controlled trial with 40 patients fulfilling criteria for ICD-10 diagnosis of alcohol dependence (F10.2), admitted for alcohol detoxification and withdrawal treatment. The benzodiazepine oxazepam was given as symptom-triggered treatment based on the scores of the Clinical Institute Withdrawal Assessment for Alcohol revised (CIWA-Ar) scale. Participants were randomized to receive either intranasal oxytocin (24 IU twice daily) or placebo. Primary outcome: Oxazepam dose required to complete a three-day course of detoxification. Secondary outcomes: Scores of the CIWA-Ar, the 10-item Hopkins Symptom Check List (HSCL-10), and self-reported total number of hours of sleep.

Results: The mean total oxazepam dose (± standard deviation) was 56.8 ± 72.8 mg in the oxytocin group and 79.0 ± 122.9 in the placebo group ($p = 0.490$; difference -22.3 mg; 95% confidence interval (CI) -86.9 to +42.4 mg). The findings were inconclusive as to whether a difference in the CIWA-Ar score (5.94 ± 3.86 vs. 6.48 ± 3.92; $p = 0.665$) or in any of the other secondary outcomes was present. No serious adverse events were reported.

Conclusion: Compared to placebo, intranasal oxytocin did not significantly reduce the oxazepam dose needed to complete a 3-day course of alcohol detoxification and withdrawal treatment.

1. Introduction

Alcohol use is a serious global health problem with high morbidity and mortality. In 2012, 3.3 million deaths or 5.9% of all deaths worldwide were attributable to alcohol consumption (WHO, 2012). Alcohol withdrawal syndrome (AWS) is a cluster of autonomic symptoms which appears within 6–24 hours after an abrupt stop or a sudden reduction in alcohol intake among heavy drinkers. The syndrome seems to be caused by an acute imbalance in the regulation of inhibitory and excitatory neurotransmitter systems, and pharmacological treatment is frequently needed. If left untreated, symptoms can progress to hallucinations, seizures, delirium tremens, or even death during the following 5–7 days (McKeon et al., 2008; Mirijello et al., 2015). Most acute symptoms usually subside within 72 h with proper treatment (Jesse et al., 2017).

Symptom-triggered administration of benzodiazepines according to a standardized treatment protocol is regarded as the treatment of choice for severe AWS (Amato et al., 2011; Daeppen et al., 2002). Through their effect on $GABA_A$ receptors, benzodiazepines are effective for short-term use in AWS (Amato et al., 2010). However, due to their potentially serious adverse effects, such as respiratory depression and dependency, use is mainly recommended during medically managed inpatient detoxification only (Mirijello et al., 2015; Rolland et al., 2016; Soyka et al., 2017).

The need for a safer and more effective treatment of AWS is evident. Such treatment should be easy to administer, have minimal adverse

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effects, and not be potentially addictive. Oxytocin nasal spray has been suggested as a pharmacological tool in substance and alcohol use disorders (Bowen and Neumann, 2017; Lee et al., 2016; Lee and Weerts, 2016; McGregor and Bowen, 2012). Oxytocin is one of the anti-stress systems involved in acute alcohol withdrawal, and is believed to exert anxiolytic and prosocial effects (Heinrichs et al., 2003; Kirkpatrick et al., 2014; Macdonald and Macdonald, 2010; Mason, 2017; Mitchell et al., 2016; Neumann and Slattery, 2016). A pilot study on alcohol withdrawal from 2013 (Pedersen et al., 2013) showed a significant reduction both in the Clinical Institute Withdrawal Assessment – Alcohol (CIWA-A) (Sullivan et al., 1989) symptom score and in the total benzodiazepine dose needed in the oxytocin group (N = 7) compared to the placebo group (N = 4).

The aim of the present study was to examine the effect of oxytocin nasal spray in acute alcohol withdrawal in a group of patients receiving hospital alcohol detoxification. The primary outcome was the total oxazepam dose required to complete a three-day course of detoxification.

2. Material and methods

The study was a double-blind, randomized placebo-controlled trial including a total of 40 patients admitted for alcohol detoxification and withdrawal treatment at the Blue Cross Lade Addiction Treatment Center (LBS) in Trondheim, Norway. 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). The trial was also approved and supported by the User Committee at LBS.

2.1. Subjects

Eligible subjects 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 normal 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 enrolment in the study. Because we wanted to replicate the only previously published study in the field (Pedersen et al., 2013), these criteria were virtually identical to those in that study. 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 $< 17\ kg/m^2$ or a history of anorexia nervosa or bulimia in the past two years; pregnancy; parturition or breastfeeding in the past six months; and the inability to read or understand Norwegian sufficiently well to complete the study questionnaires. In addition, patients were excluded if the alcohol breath test was negative, and the time interval since the last alcohol intake was more than 15 h.

2.2. Medication

Empty nasal spray bottles and pumps were acquired from Wirth Emballage, Åkersberga, Sweden. Oxytocin nasal spray (Syntocinon; Alfasigma 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.

2.3. Randomization

Randomization was performed using a web-based randomization system developed and administered by the Unit of Applied Clinical Research at the Norwegian University of Science and Technology – NTNU in Trondheim, Norway. Once a new study subject was included, the system generated a nasal spray number corresponding to one nasal spray portion numbered by the manufacturer. Randomization was undertaken in a 1:1 ratio.

2.4. Intervention

On the first study day, written informed consent was obtained from all patients who met the inclusion criteria but not the exclusion criteria. If subjects were visibly intoxicated or experiencing moderate withdrawal at admission, the informed consent procedure was repeated the following day. Patients were assessed with the CIWA-Ar immediately after admission. All patients underwent a physical examination. Blood for routine biochemical testing, including testing for the alcohol marker phosphatidylethanol (PEth), and urine for the analysis of drugs of abuse were collected. Finally, the subjects were instructed on how to fill out the inpatient diary containing questions about sleep.

At the time of each administration, subjects were given six insufflations of the nasal spray (containing a total dose of 24 IU oxytocin or placebo) in interchanging nostrils with 15 s in between insufflations. The use of nasal spray 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 administered the nasal sprays at the ward twice daily at 9 a.m. and 6 p.m. Thus, during the 3-day course of treatment, a maximum of 6 administrations of nasal spray could be given. A deviation of ± 2 h from the scheduled times of administration was considered acceptable. Some patients received one administration on day one due to late admission.

On day two, study nurses interviewed the patients using the Timeline Follow-Back (TLFB) (Sobell et al., 1988) to assess their alcohol intake during the last 14 days prior to admission.

Day three was the last study day. Subjects answered the Hopkins Symptom Check List-10 (HSCL-10) (Strand et al., 2003).

2.5. Outcome measures and endpoints

The primary endpoint was the cumulative oxazepam dose given during the three first days of detoxification. Secondary endpoints were the CIWA-Ar scores, HSCL-10 scores, and self-reported sleep. CIWA-Ar scoring, which was a prerequisite for the administration of oxazepam, was conducted in the following manner: If the CIWA-Ar score was 15 or above, 15 mg oxazepam was given, and the scoring was repeated after 1 h. If the CIWA-Ar score was 10–14, 10 mg oxazepam was given, and the scoring was repeated after 1 h. If the CIWA-Ar score was below 10, no oxazepam was given, and the scoring was repeated after 4 h. The CIWA-Ar protocol was ended if the score was below 10 in two consecutive assessments or if the score was below 10 and more than 48 h had passed since the last alcohol intake. Additional oxazepam could be given for emergency purposes at the discretion of the attending physician. If a patient had to be given diazepam for administrative reasons, the diazepam dose was converted to oxazepam by using a factor of 2 (Ashton, 2002a). Apart from oxazepam and diazepam, no other benzodiazepine treatment was provided. Mean CIWA-Ar scores and the total oxazepam dose administered each day as well as in the whole 3-day-period were calculated.

The standard detoxification protocol also included the administration of thiamine as well as other vitamin and mineral supplementation.

2.6. Statistical analyses

The power calculation was based upon the only previously

published study of effects of intranasal oxytocin on benzodiazepine consumption during alcohol withdrawal (Pedersen et al., 2013). Detection of a difference of 10 mg in oxazepam consumption between groups was considered to be of clinical interest. Given an expected standard deviation of approximately 10 mg, power > 0.80 and alpha < 0.05, 16 subjects in each group should be needed. We, therefore, chose to include a total of 40 patients in the study.

Baseline characteristics of the two groups were compared using independent samples t-tests for continuous data and chi-square tests for categorical data. The mean treatment effect was considered to be the most relevant efficacy measure. The sample averages for the two treatment groups were considered to be approximately normally distributed by the central limit theorem and light tailed distributions for individual observations. Therefore, treatment effects on outcome variables were tested using independent samples t-tests. All statistical tests were two-tailed, and p values < 0.05 were considered statistically significant. Statistical analyses were performed with IBM SPSS Statistics 23 (IBM Corp., 2012). Patients, clinical personnel, researchers and statistician were blinded to group allocation until the statistical calculations were finished.

3. Results

The inclusion period lasted from October 2016 to November 2017. The enrolment of study participants and their completion according to the study protocol are shown in Fig. 1. Thirty-nine of the 40 included subjects (97.5%) completed the 3-day intervention. The last patient left the treatment center prematurely, but close to the end of the treatment period. At that time, he had completed the CIWA-Ar protocol with two consecutive scores < 10 and also finished the oxazepam treatment period. Oxazepam and CIWA-Ar data for this participant are therefore included in the analyses. However, as he did not complete the questionnaire on day three, his data are not included in the HSCL-10 and sleep analyses.

Demographical and clinical characteristics of the patients are displayed in Table 1. There were no significant differences between the study groups for any of these characteristics, nor when further dividing them into subgroups of high and low alcohol intake (> 16 units and ≤16 units) and high and low PEth (> 2 μmol/L and ≤2 μmol/L). Five subjects, of whom three had been randomized to the placebo group and two to the oxytocin group, were given treatment with diazepam instead of oxazepam, either due to a history of seizures or an insufficient effect from oxazepam.

There were no statistically significant differences in the total oxazepam dose administered, mean CIWA-Ar scores or any other outcome variable between the two groups, as seen in Table 2. Daily oxazepam doses are displayed in Fig. 2, and daily mean CIWA-Ar scores are depicted in Fig. 3. There were no significant differences between the groups in any of these measures.

Seven patients in the oxytocin group and nine patients in the placebo group did not receive any oxazepam during the 3-day period. There were large interindividual variations in cumulative oxazepam doses administered (range 0–510 mg). One patient in the oxytocin group received a total dose of 300 mg, whereas one patient in the placebo group received a total dose of 510 mg. However, no significant difference in oxazepam dose between groups was found even when excluding the two high-dose outliers. Moreover, the results were principally the same when the patients who did not receive any oxazepam were excluded.

We also reanalyzed data after dividing the participants into subgroups of those with self-reported daily alcohol intake of > 16 units and ≤16, according to the previously published study (Pedersen et al., 2013). Across all participants, i.e., irrespective of whether the patients received oxytocin or placebo, there was a significant difference both in the oxazepam dose given (35.8 mg vs. 115.9 mg, p = 0.031) and the CIWA-Ar score (4.77 vs. 8.37, p = 0.004) between those with an alcohol intake of > 16 units (n = 16) and ≤ 16 units (n = 24). The oxazepam doses appeared to be reduced to a larger degree by oxytocin in the group with the higher alcohol intake (83.5 mg in the oxytocin group vs. 170.0 mg in the placebo group) than in the group with the lower alcohol intake (30.0 mg in the oxytocin group vs. 40.0 mg in the placebo group), but these differences were not statistically significant (p = 0.299 and p = 0.676, respectively). The tendency was the same for CIWA-Ar scores (7.62 in the oxytocin group vs. 9.61 in the placebo group in those with an intake of > 16 units; 4.27 in the oxytocin group vs. 5.14 in the placebo group in those with an intake of ≤16 units; p = 0.314 and p = 0.533, respectively). When restricting patients to those with a PEth concentration > 2 μmol/L the mean oxazepam dose was 81.5 mg in the oxytocin group and 85.6 mg in the placebo group (p = 0.947) and the mean CIWA-Ar score was 6.98 in the oxytocin group and 5.90 in the placebo group (p = 0.597). Among those with a PEth concentration ≤ 2 μmol/L the mean oxazepam dose was 32.0 mg in the oxytocin group and 65.5 mg in the placebo group (p = 0.273) and the mean CIWA-Ar score was 4.91 in the oxytocin group and 6.57 in the placebo group (p = 0.303).

No adverse effects considered to be related to the study drug were reported. Mild discomfort due to the large volume of insufflations was reported in both treatment groups.

4. Discussion

The principal finding in the present study is that there was no statistically significant difference in the oxazepam dose needed to complete a 3-day course of alcohol detoxification and withdrawal treatment between the oxytocin group and the placebo group. In addition, there were no statistically significant differences in CIWA-Ar scores, HSCL-10 scores, or hours of self-reported sleep.

The results from our study contrast those in the only previously published study of oxytocin in AWS (Pedersen et al., 2013), where the mean lorazepam dose in the oxytocin group (3.4 ± 4.7 mg) was about one-fifth of that in the placebo group (16.5 ± 4.4 mg; p = 0.0015). As one mg lorazepam equals 20 mg oxazepam (Ashton, 2002b), these doses correspond to oxazepam doses of 68 ± 94 mg and 330 ± 88 mg, respectively. Thus, the mean oxazepam dose in the oxytocin group was about the same in the two studies. In contrast, the mean dose in the placebo group was considerably lower in the present study than in the study of Pedersen et al., but the intra-group variability was larger. In the Pederson et al. study, the mean CIWA score was significantly lower in the oxytocin group than the placebo group on day 1 (4.3 vs. 11.8; p < 0.0001) and on day 2 (3.4 vs. 11.1; p = 0.0015) but not on day 3 (3.1 vs. 5.4; p = 0.119). No such differences were found in the present study (Fig. 3).

The authors of the previous study (Pedersen et al., 2013) also compared a subgroup of patients with a self-reported daily alcohol intake of ≤ 16 units (n = 4 in both groups) and found that the patients in the oxytocin group did not require any lorazepam at all, whereas those in the placebo group received a mean dose of 16.5 mg (p = 0.005). Moreover, the daily mean CIWA scores were significantly lower in the oxytocin group than in the placebo group on all three days. Again, we did not find any significant differences in oxazepam dose or in CIWA-Ar scores neither in those with an alcohol intake of ≤ 16 units nor in those with an alcohol intake of > 16 units, although there was a trend that the reduction both in oxazepam doses and in CIWA-Ar scores in the oxytocin group was more pronounced among those with higher alcohol intake than among those with lower alcohol intake.

Although our aim was to replicate the previously published study (Pedersen et al., 2013) as closely as possible, there are some differences that should be highlighted. The only principal difference in the inclusion criteria was that we also included patients with a history of severe or complicated alcohol withdrawal. This fact could have contributed to the increase in oxazepam dose needed by some patients, thereby possibly explaining some of the large interindividual variation in oxazepam

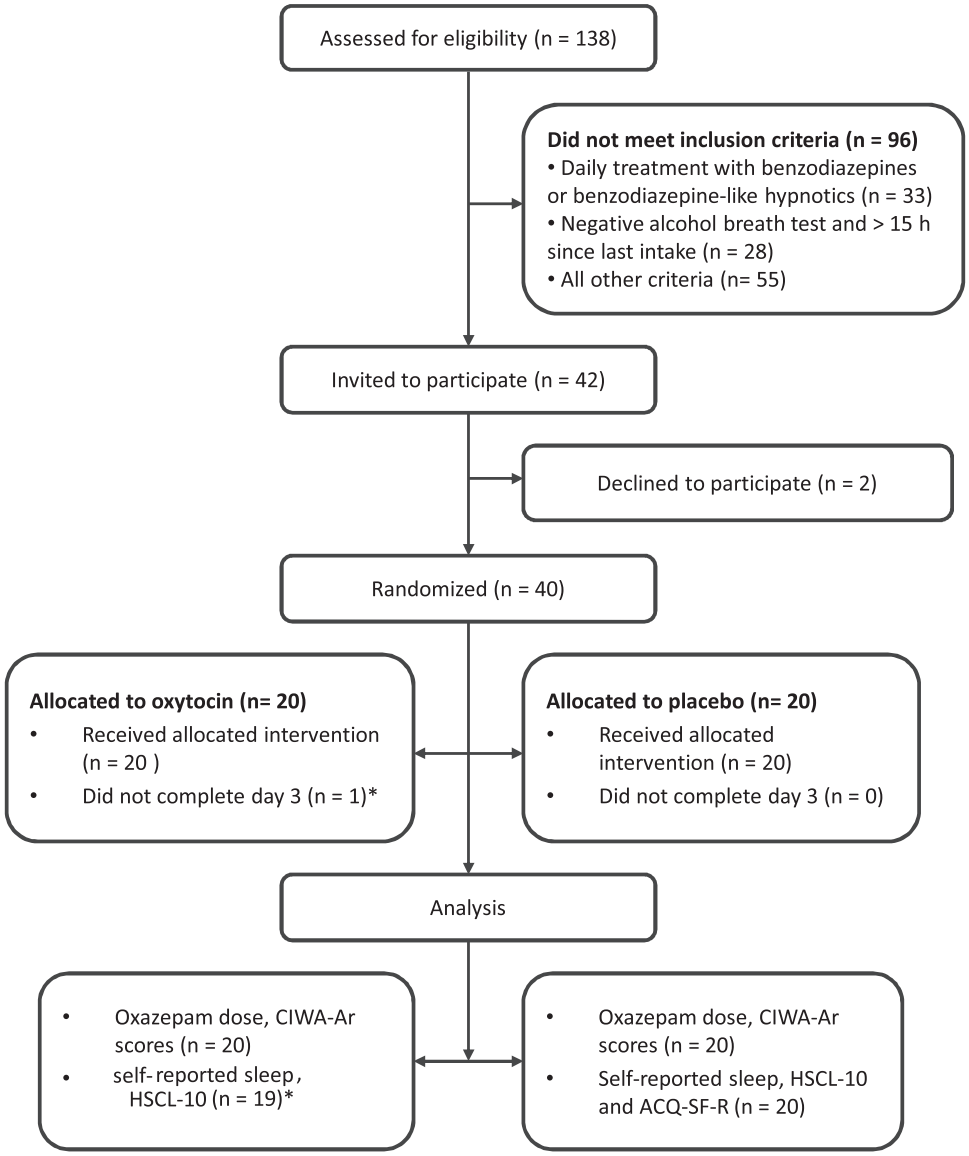

Fig. 1. Flow chart of the inclusion of patients and completion of the study according to the Consolidating Standard of Reporting Trials (CONSORT). *One subject left the treatment center after he had completed the CIWA-Ar protocol and finished oxazepam treatment but before the final assessments on day 3.

dose, and perhaps even more so in the placebo group than in the oxytocin group.

We used the CIWA-Ar, i.e., the revised 11-item version with a maximum score of 67, whereas the other study used the original 15-item CIWA with a maximum score of 98. The two protocols also differed somewhat with regard to the cut-off scores for giving benzodiazepines and the doses of benzodiazepines administered for a given score. Moreover, in our study, the frequency of the scorings was not fixed but depended on the severity of the symptoms in the individual patient. It should also be noted that there was a minor difference between the

Table 1
Baseline characteristics and clinical data of 40 patients with alcohol withdrawal syndrome randomized to treatment with either oxytocin nasal spray or placebo.

	Oxytocin group (n = 20)	Placebo group (n = 20)	P value
Gender (males/females)	13/7	16/4	0.288
Age (years), mean ± SD	48.9 ± 11.3	46.6 ± 9.7	0.503
Marital status (single/cohabiting)	14/6	14/6	1.00
Employed (yes/no)	5/15	4/16	0.705
Self-reported daily alcohol intake during the last 14 days (standard alcohol units[a]), mean ± SD	17.0 ± 8.0	15.0 ± 6.4	0.399
Phosphatidylethanol blood concentration at inclusion (μmol/L), mean ± SD	2.26 ± 1.12	2.20 ± 1.22	0.871
Total number of hours in the study, mean ± SD	53.4 ± 5.5	52.4 ± 9.2	0.681
Total number of nasal spray administrations, mean ± SD	5.80 ± 0.41[b]	5.90 ± 0.31[c]	0.389

SD = standard deviation.
[a] One standard alcohol unit corresponds to 12.8 g ethanol.
[b] Four patients received five nasal spray administrations, 16 patients received six nasal spray administrations.
[c] Two patients received five nasal spray administrations, 18 patients received six nasal spray administrations.

Table 2
Key outcome data of 40 patients with alcohol withdrawal syndrome randomized to treatment with either oxytocin nasal spray or placebo.

	Oxytocin group (n = 20)	Placebo group (n = 20)	P value	Difference[a] (95 % CI)
Total oxazepam dose (mg), mean ± SD	56.8 ± 72.8	79.0 ± 122.9	0.490	−22.3 (-86.9 to 42.4)
CIWA-Ar[b] score, mean ± SD	5.94 ± 3.86	6.48 ± 3.92	0.665	−0.54 (-3.03 to 1.95)
HSCL-10[c] score, mean ± SD	25.1 ± 5.6	25.3 ± 7.3	0.945	−0.15 (-4.38 to 4.09)
Self-reported sleep[d] (hours), mean ± SD	5.28 ± 2.95	5.92 ± 3.17	0.535	−0.64 (-2.72 to 1.44)

CI = confidence interval and SD = standard deviation.
[a] Mean value in the oxytocin group minus mean value in the placebo group.
[b] Clinical Institute Withdrawal Assessment – Alcohol revised.
[c] Hopkins Symptom Check List −10.
[d] Mean numbers of hours of sleep calculated as the number of sleeping hours from day 1 to day 2 plus the number of sleeping hours from day 2 to day 3 divided by 2.

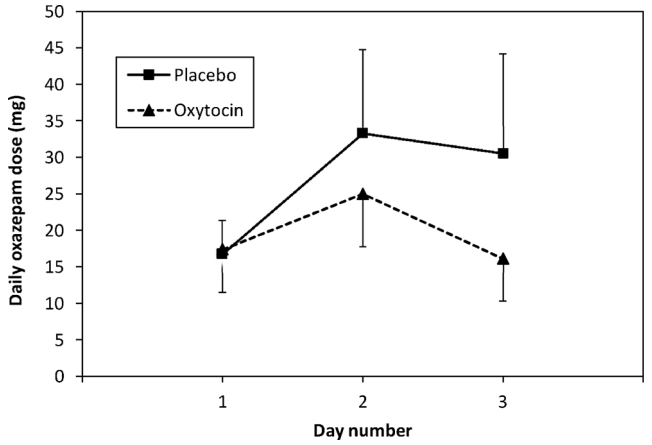

Fig. 2. Daily oxazepam dose administered in 40 patients with alcohol withdrawal syndrome randomized to treatment with either oxytocin nasal spray (n = 20) or placebo (n = 20) during a three-day course of treatment. Data are presented as the mean ± standard error of the mean. None of the differences were statistically significant (day 1: 17.4 vs. 16.8 mg, p = 0.93; day 2: 25.0 vs. 33.3 mg, p = 0.55; day 3: 16.1 vs. 30.5 mg, p = 0.34).

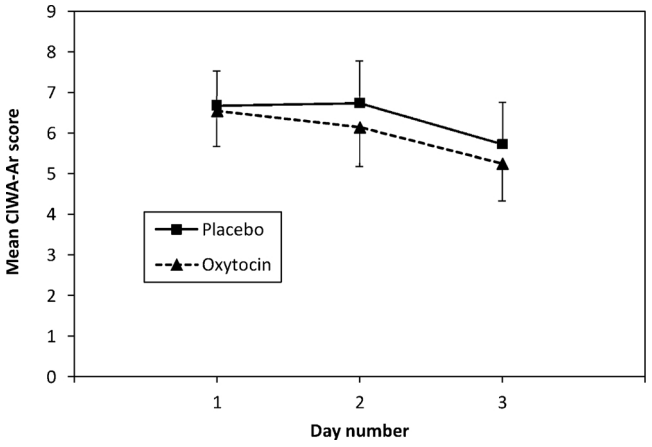

Fig. 3. Daily mean Clinical Institute Withdrawal Assessment – Alcohol revised (CIWA-Ar) score in 40 patients with alcohol withdrawal syndrome randomized to treatment with either oxytocin nasal spray (n = 20) or placebo (n = 20) during a three-day course of treatment. Data are presented as the mean ± standard error of the mean. None of the differences were statistically significant (day 1: 6.55 vs. 6.68, p = 0.92; day 2: 6.15 vs. 6.74, p = 0.69; day 3: 5.25 vs. 5.73, p = 0.73).

studies with respect to the administration of nasal spray, as the insufflations were given 15 s apart instead of 30 s, in the present study.

Another obvious difference is the type of benzodiazepine used. The other study used lorazepam, whereas we used oxazepam, which also has a short elimination half-life but a somewhat slower onset of action (Ashton, 2002a,b). We chose to use oxazepam because that drug was the standard treatment, and the staff was familiar with this drug. The CIWA-Ar scores appeared to be relatively low in all the patients, indicating a possibility that oxytocin might not be efficacious in alcohol dependent patients with mild alcohol withdrawal.

Although the difference in the mean oxazepam dose between the oxytocin group and the placebo group was numerically more than twice the predefined value of 10 mg, the difference was not statistically significant. Even more visually striking (Fig. 2), but still not statistically significant, is that the mean oxazepam dose in the oxytocin group at day 3 appeared to be only about half of that in the placebo group. One explanation for the non-significant results could be the considerable and unexpected interindividual variability in oxazepam doses within the two groups, particularly in the placebo group, which resulted in what could be considered an underpowered trial. Notably, the confidence interval for the difference in total oxazepam dose was very wide, ranging from almost a 90 mg reduction in favor of oxytocin to a more than 40 mg reduction in favor of placebo.

It is puzzling that even though the only previously published study included no more than 11 patients, large and statistically significant positive effects of oxytocin were shown (Pedersen et al., 2013), whereas the present study, which included a total of 40 patients, failed to replicate this finding. Although there were a number of differences in design between the two studies, we find it unlikely that these differences, with the possible exception of the inclusion of patients with a history of severe or complicated withdrawal in the present study, can explain the contrasting results in the two studies. Thus, we are unable to find any clear-cut and convincing reasons for the observed discrepancies.

The patients tolerated oxytocin well, and there were no serious adverse effects observed during the trial. This finding is consistent with the fact that no serious adverse effects have been reported after intranasal use of oxytocin in clinical trials over the last 20 years (MacDonald et al., 2011). Nevertheless, no other drugs, including oxytocin, have proven to be as effective as benzodiazepines in reducing the risk of alcohol withdrawal seizures and delirium tremens (Amato et al., 2010; Daeppen et al., 2002; Rolland et al., 2016). Thus, benzodiazepines are still considered the safest and most effective treatment of severe alcohol withdrawal.

In addition to the previously discussed power issue due to the unexpected interindividual variability in oxazepam use, there are also some other weaknesses that should be acknowledged. We did not register the length of alcohol addiction before inclusion, or previous diagnoses of anxiety, and we did not genotype the patients for oxytocin receptor polymorphisms, all of which are variables thought to be of importance in evaluating the effects of oxytocin in previous studies (Love et al., 2018; Mitchell et al., 2016; Vaht et al., 2016). Moreover, we have only investigated one specific dosage schedule of oxytocin, and higher doses and/or more frequent dosing could have generated other results. On the other hand, there are several strengths in the present

study. One is the rigorous design of the study with a negligible risk of unblinding, and another is the high rate of participation and completion by patients who met the inclusion criteria and did not have any exclusion criteria. Selection bias within the patient group is therefore considered to be low. Positive reinforcement through close monitoring and a high level of attention to study subjects could be a part of the reason why so many patients completed the trial. In fact, the only drop-out took place towards the very end of the 3-day treatment period. In addition, before the study started, the ward had well-established routines for using the CIWA-Ar protocol and for using oxytocin in withdrawal treatment, and the staff was familiar with all procedures involved.

Increased stress and anxiety are clinical symptoms frequently seen in acute alcohol withdrawal, where the severity of withdrawal is further enhanced in patients with an underlying diagnosis of anxiety (Johnston et al., 1991). The exclusion criterion of daily use of benzodiazepines or benzodiazepine-like hypnotics precluded many patients from being included (n = 33), showing that the combination of alcohol and sedatives is frequently seen in patients with alcohol use disorder. Intranasal oxytocin has been shown to be anxiolytic in patients with generalized anxiety disorder and social anxiety (de Oliveira et al., 2012; MacDonald and Feifel, 2014; Neumann and Slattery, 2016). In our study, all but three patients in each treatment group obtained HSCL-10 scores above the cut-off level of 1.85, indicating that the majority of the included patients presented a clinical appearance of anxiety and/or depression-like symptoms during withdrawal. Similarly, in a previous trial, the mean HSCL-10 score at admission was 2.54 (Hoxmark et al., 2010).

There are still many unanswered questions related to the use of intranasal oxytocin in substance use disorders as well as in other psychiatric disorders. These questions include its exact mechanism of action, how it enters the central nervous system after intranasal administration (Neumann et al., 2013) and how dose-related measurements of oxytocin could be performed, as the concentrations of peripheral oxytocin do not seem to correlate with central oxytocin concentrations (Valstad et al., 2017; Walum et al., 2016).

5. Conclusion

In this trial, intranasal oxytocin did not significantly reduce the oxazepam dose needed to complete a 3-day course of alcohol detoxification and withdrawal treatment. Nonetheless, research on oxytocin in substance and alcohol use disorder is yet in an early phase, and further studies are urgently needed to clarify whether intranasal oxytocin has a place in the treatment of AWS.

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Contributors

The authors have contributed to the paper as follows: Design and protocol: KM, RWG, TA, OS. Obtaining of data: KM. Calculations and analyses: KM and ØS, with input from OS. Preparation of the manuscript: KM, RWG, TA, and OS, with input from ØS. All authors have approved the final version of the manuscript.

Conflict of interest

No conflict declared.

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