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Intranasal Oxytocin to Prevent Posttraumatic Stress Disorder Symptoms: A Randomized Controlled Trial in Emergency Department Patients

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ABSTRACT

BACKGROUND: There are currently few preventive interventions available for posttraumatic stress disorder (PTSD). Intranasal oxytocin administration early after trauma may prevent PTSD, because oxytocin administration was previously found to beneficially impact PTSD vulnerability factors, including neural fear responsiveness, peripheral stress reactivity, and socioemotional functioning. Therefore, we investigated the effects of intranasal oxytocin administration early after trauma on subsequent clinician-rated PTSD symptoms. We then assessed whether baseline characteristics moderated the intervention's effects.

METHODS: We performed a multicenter, randomized, double-blind, placebo-controlled clinical trial. Adult emergency department patients with moderate to severe acute distress ($n = 120$; 85% accident victims) were randomized to intranasal oxytocin (8 days/40 IU twice daily) or placebo (8 days/10 puffs twice daily), initiated within 12 days posttrauma. The Clinician-Administered PTSD Scale (CAPS) was administered at baseline (within 10 days posttrauma) and at 1.5, 3, and 6 months posttrauma. The intention-to-treat sample included 107 participants (oxytocin: $n = 53$; placebo: $n = 54$).

RESULTS: We did not observe a significant group difference in CAPS total score at 1.5 months posttrauma (primary outcome) or across follow-up (secondary outcome). Secondary analyses showed that participants with high baseline CAPS scores receiving oxytocin had significantly lower CAPS scores across follow-up than participants with high baseline CAPS scores receiving placebo.

CONCLUSIONS: Oxytocin administration early after trauma did not attenuate clinician-rated PTSD symptoms in all trauma-exposed participants with acute distress. However, participants with high acute clinician-rated PTSD symptom severity did show beneficial effects of oxytocin. Although replication is warranted, these findings suggest that oxytocin administration is a promising preventive intervention for PTSD for individuals with high acute PTSD symptoms.

Keywords: Early intervention, Intranasal oxytocin, Prevention, Psychotrauma, PTSD, RCT

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Posttraumatic stress disorder (PTSD) is a debilitating psychiatric disorder associated with impaired well-being, high psychiatric and physical comorbidity and increased mortality, and therefore high societal burden (1,2). By definition, trauma exposure represents an identifiable precipitating event of PTSD, and there is a potential for administering preventive interventions in the early phase posttrauma to mitigate long-term adverse outcomes. Only a few interventions administered early after trauma currently have been shown to reduce subsequent PTSD symptom development. The protective effects of prolonged exposure (3) and hydrocortisone (4,5) on PTSD development were observed in acutely trauma-exposed patients in the emergency department (ED), in which treatment was initiated within 6 to 12 hours posttrauma. Furthermore, brief cognitive behavioral therapy was found to reduce PTSD symptom development in individuals with acute stress disorder (6).

In recent years, it was observed that autonomic and glucocorticoid reactivity to stress, assessed prior to or early after trauma, predicts PTSD symptom development (7,8). Also, neural threat processing before and early after trauma was found to predict subsequent PTSD (9–11). In addition, low perceived social support early after trauma has been associated with increased PTSD risk (12,13). Targeting these vulnerability factors before

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development of the full-blown constellation of PTSD symptoms may prevent long-term adverse outcomes and promote adaptive recovery.

Intranasal administration of the neuropeptide oxytocin may be a promising pharmacological agent to prevent PTSD (14,15). Accumulating evidence from studies in animals and in healthy and psychiatric human populations shows that oxytocin administration may modulate glucocorticoid (16) and autonomic stress reactivity (17), dampen anxiety and neural threat processing (18,19), and beneficially impact socioemotional processes and prosocial behavior (20,21) [but see also (22,23) for seemingly nonprosocial effects]. Furthermore, in patients with PTSD, a single oxytocin administration decreased state anxiety (24) and normalized neural reactivity of key brain areas involved in threat processing [i.e., decreased amygdala reactivity to emotional faces (25)], and normalized aberrant resting state functional connectivity between amygdala subregions and prefrontal and salience processing areas to the level of traumatized individuals without PTSD (24).

It has not yet been investigated whether oxytocin administration early after trauma may prevent PTSD development. Preclinical studies administering oxytocin once shortly after severe stress have provided mixed results. In rats, central oxytocin administration either immediately or 7 days after a severe stressor reduced PTSD-like behavior (freezing behavior, acoustic startle response, time spent in enclosed arms of elevated plus maze) 1 week later (26). In recently trauma-exposed individuals, however, intranasal oxytocin within 10 days posttrauma increased amygdala reactivity to fearful faces (27) and decreased amygdala-ventrolateral prefrontal functional connectivity after a trauma reminder (28). These results indicate that effects of oxytocin administration in recently trauma-exposed individuals may not be beneficial. However, actual clinical effects were not investigated. Moreover, a recent rodent study showed that while a single subcutaneous administration of oxytocin immediately after a severe stressor increased contextual fear memory during re-exposure to the stressor context after 2 days without affecting subsequent fear behavior, both repeated and chronic subcutaneous oxytocin administration for 7 or 14 days poststressor resulted in decreased fear generalization after 14 days (29). This indicates that the effects of a single oxytocin administration may differ from the effects of repeated administration and suggests that repeated oxytocin administration may be required to achieve clinically relevant effects regarding the prevention of PTSD.

We conducted a randomized placebo-controlled clinical trial in recently trauma-exposed acutely distressed ED patients, in which our primary aim was to assess the effects of repeated oxytocin administration on clinician-rated PTSD symptom severity at 1.5 months posttrauma. Secondarily, we investigated the effects of repeated oxytocin administration on clinician-rated PTSD symptom severity at 3 and 6 months posttrauma, as well as the effects of oxytocin administration on self-reported PTSD and depression and anxiety symptoms across follow-up. We hypothesized that oxytocin administration would be associated with more favorable psychological outcomes at follow-up compared to placebo. Finally, we assessed whether baseline characteristics moderated the observed effects of oxytocin administration. At the time of study design, it had been demonstrated that interindividual differences in early attachment experiences and socioemotional and cognitive proficiency moderated the effects of a single oxytocin administration on socioemotional functioning (30). More recently, several studies have demonstrated that the presence and severity of psychiatric symptoms also moderate the effects of a single oxytocin administration (16,31,32). In addition, the effects of a single oxytocin administration in psychiatric patients were shown to depend on the patients' sex (24) and trauma history (33,34). In view of our study population and these more recent findings, we decided to investigate whether the effects of repeated oxytocin administration were moderated by sex, childhood trauma, and symptom severity before the start of the intervention.

METHODS AND MATERIALS

Design

This was a multicenter, double-blind, randomized placebo-controlled trial. The randomization and blinding procedures are shown in Supplemental Methods, and a graphical overview of the study design is shown in Figure 1. All study procedures were performed by researchers of the Academic Medical Center, Amsterdam, the Netherlands.

The study was approved by the Institutional Review Board of the Academic Medical Center, Amsterdam, the Netherlands, and registered at the Netherlands Trial Registry. Good Clinical

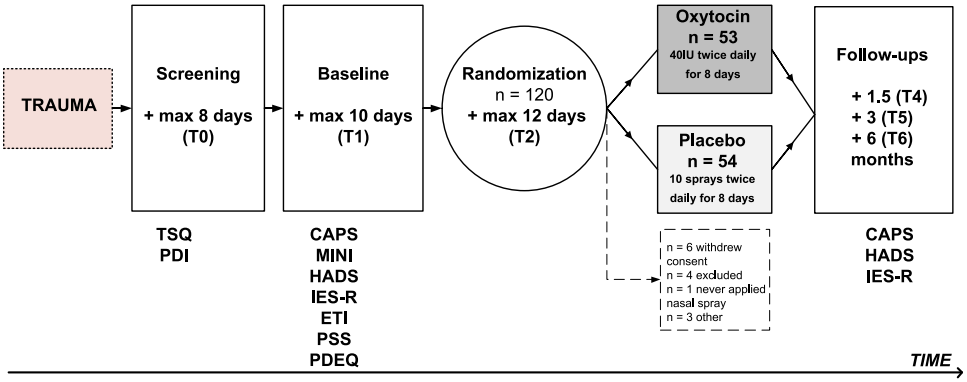

Figure 1. Overview of the study design. CAPS, Clinician-Administered PTSD Scale; ETI, Early Trauma Inventory; HADS, Hospital Anxiety and Depression Scale; IES-R, Impact of Events Scale-Revised; MINI, Mini-International Neuropsychiatric Interview; PDEQ, Peritraumatic Dissociative Experiences Questionnaire; PDI, Peritraumatic Distress Inventory; PSS, Perceived Stress Scale; TSQ, Trauma Screening Questionnaire.

Practice guidelines were followed during all procedures. Quality monitoring was performed by an independent monitor.

Participants

We included patients visiting one of three participating EDs in Amsterdam, the Netherlands (academic level 1 trauma centers: Academic Medical Center, VU University Medical Center; level 2 trauma center: Onze Lieve Vrouwe Gasthuis Hospital West) after experiencing a traumatic event (DSM-IV PTSD A1 criterion) (35). Adults (18–65 years of age) scoring above screening questionnaire cutoffs indicating moderate to severe acute distress and hence increased PTSD risk were eligible (see Study Procedures below). Exclusion criteria were current PTSD or depression; psychotic, bipolar, substance-related, and personality disorder; severe/chronic systemic disease; mental retardation; neurological/endocrine disorder; ongoing traumatization; medications potentially interfering with oxytocin administration (e.g., systemic glucocorticoids or psychotropic medications); oxytocin allergy; persistent impaired consciousness or amnesia; pregnancy; and breastfeeding.

Study Procedures

Screening, Enrollment, and Baseline Assessment. After verbal consent, trauma-exposed ED patients provided a brief description of their recent traumatic event (used to categorize trauma type) and were screened for peritraumatic and immediate distress within 8 days posttrauma (T0) (mean [SD] = 3.43 [1.90] days), using the Trauma Screening Questionnaire (TSQ) (36) and the Peritraumatic Distress Inventory (PDI) (37). Individuals scoring above TSQ or PDI cutoffs [TSQ $\geq$ 5 (38,39); PDI $\geq$ 17 (40)], indicating increased PTSD risk, were invited to participate [see Supplemental Methods on measures and our previously published protocol (41) for more details on cutoff selection].

At baseline (T1, within 10 days posttrauma; mean [SD] = 6.51 [1.76] days), written and verbal informed consent was obtained and current and lifetime psychopathology [Mini-International Neuropsychiatric Interview (42,43)] and clinician-rated acute PTSD symptom severity [Clinician-Administered PTSD Scale (CAPS) (44,45)] were assessed. Participants additionally completed self-report questionnaires on demographics, peritraumatic dissociation [Peritraumatic Dissociation Experience Questionnaire (46)], acute PTSD [Impact of Event Scale–Revised (IES-R) (47)], depression and anxiety symptoms [Hospital Anxiety and Depression Scale (HADS) (48,49)], childhood trauma [Early Trauma Inventory, short version (50)], and perceived stress [Perceived Stress Scale (51)]. For details on measures, see Supplemental Methods.

Intervention. Within 12 days posttrauma (T2; mean [SD] = 8.94 [1.80] days), participants administered the first dose of their allocated intervention under experimenter supervision using a pump-actuated device (i.e., intranasal oxytocin [40 IU/dose, five puffs of 4 IU per nostril] prepared by Defiante Farmaceutica, Funchal, Portugal and relabeled by Slotervaart Hospital Pharmacy, Amsterdam, the Netherlands) or placebo (0.9% NaCl solution, five puffs per nostril [prepared and labeled by Slotervaart Hospital Pharmacy, Amsterdam, the Netherlands]). Considerations regarding the oxytocin treatment regimen and participant instructions can be found in the Supplemental Methods. For the following 7 days, participants applied their allocated intervention twice daily (morning and evening). Participants recorded their self-reported administration time and potential adverse effects in a diary. Subjective intervention allocation awareness was self-reported in the diary after the final dose. Study medication was prepared under Good Manufacturing Practice license, with identical containers and labels for both conditions.

Follow-up Assessments. In-person follow-up occurred at 1.5 (T4; mean [SD] = 47.79 [7.09] days), 3 (T5; mean [SD] = 96.06 [10.44] days), and 6 months posttrauma (T6; mean [SD] = 190.39 [14.61] days). During each follow-up assessment, clinician-rated PTSD symptom severity was assessed with the CAPS (T4: primary outcome; T5 and T6: secondary outcomes). In addition, during each follow-up assessment participants self-reported on current symptom severity of PTSD (IES-R), depression, and anxiety (HADS) (secondary outcomes). Furthermore, adverse events and mental health care and medication use were inquired upon. Participants received €25 and travel expenses for each completed assessment upon initiating the intervention.

Statistical Analyses

All analyses were conducted on intention-to-treat basis in SPSS software (version 22; IBM Corp., Armonk, NY).

Demographic, trauma, and baseline clinical and intervention characteristics were compared between conditions using two-sample *t* tests for normally distributed continuous variables, Mann-Whitney *U* tests for nonnormally distributed variables, and χ^2 or Fisher's exact tests for categorical variables.

Square root transformations were applied to all CAPS, IES-R, and HADS data at follow-up because these distributions were positively skewed and no adequate nonparametric test alternative was available.

A preplanned interim analysis for our primary outcome, clinician-rated PTSD severity (CAPS total score) at T4, was performed after 50% (n = 110) of the planned included participants received the allocated nasal spray to evaluate the presence and direction of the intervention's effect [for a priori power calculation, see our published protocol (41); the institutional review board protocol, including preplanned interim analysis, is available from the authors upon request]. We performed a two-sample *t* test to investigate differences between conditions using nonimputed data. The conditional power to detect a significant difference within the planned sample was calculated from the mean difference, standard deviations, and resulting *t* value, with conditional power $<$ 0.20 indicating futility (52).

For secondary and exploratory analyses, pooled results of 40 generated datasets using multiple imputation for missing outcome data (CAPS, IES-R, and HADS) are reported (auxiliary variables: intervention, demographic, trauma, and baseline clinical characteristics) (53).

We first analyzed group differences in total CAPS scores across follow-up using linear mixed models with all included factors specified as fixed (maximum likelihood, first order autoregressive covariance structure). Intervention effects on intercept (random effect, time centered at T4) and linear slope

Table 1. Demographic, Trauma and Screening, Baseline Clinical, and Trial Characteristics for Oxytocin and Placebo Conditions

Variables	Oxytocin (n = 53)	Placebo (n = 54)	p Value
Demographics			
Age at time of event, years	35.00 (13.13)	35.91 (13.30)	.723[a]
Sex (females)	27 (50.94%)	26 (48.14%)	.772[b]
Educational level			.436[b]
Low	13 (25.5%)	14 (27.5%)	
Middle	22 (43.1%)	16 (31.4%)	
High	16 (31.4%)	21 (41.2%)	
Marital status			.450[c]
Married/cohabiting	19 (37.3%)	27 (50.9%)	
Relationship, living apart	11 (21.6%)	10 (18.9%)	
Single	20 (39.2%)	14 (26.4%)	
Other (widowed/divorced)	1 (2.0%)	2 (3.8%)	
Dutch origin	38 (74.5%)	40 (75.5%)	.910[b]
Trauma and Screening Characteristics			
Type of trauma			.261[b]
Accidental	43 (81.13%)	48 (88.89%)	
Assault	10 (18.87%)	6 (11.11%)	
TSQ Total score T0	6.08 (1.95)	5.96 (2.18)	.779[a]
PDI Total score T0	20.75 (8.86)	21.81 (7.61)	.508[a]
Baseline Clinical Characteristics			
CAPS Total T1	42.83 (16.93)	41.28 (20.96)	.675[a]
CAPS Total T1 ≥45	23 (43.4%)	20 (37.0%)	.502[b]
IES-R Total score T1	34.68 (19.55)	33.71 (21.08)	.811[a]
HADS-Anxiety score T1	7.54 (4.68)	6.79 (3.94)	.382[a]
HADS-Depression score T1	5.44 (3.98)	5.75 (4.29)	.752[d]
PSS Total score T1	15.40 (7.40)	13.79 (6.07)	.230[a]
PDEQ Total score T1	25.30 (10.21)	25.87 (7.77)	.753[a]
Probable lifetime PTSD	8 (15.4%)	5 (9.4%)	.390[b]
ETI childhood trauma total score	6.12 (4.19)	4.96 (4.09)	.116[d]
Trial Characteristics			
Dropout (no follow-up at all)	8 (15.1%)	6 (11.3%)	.541[b]
Nasal spray (reported doses administered)	14.24 (2.18)	13.43 (2.65)	.017[d]
Subjective intervention allocation awareness			.316[c]
Oxytocin	7 (20%)	9 (22.5%)	
Placebo	20 (57.1%)	27 (67.5%)	
"Don't Know"	8 (22.9%)	4 (10%)	
Mental health care use	10 (23.8%)	11 (22.9%)	.920[b]
Psychopharmaceuticals use	3 (6.7%)	7 (14.6%)	.319[c]

Values are n (%) or mean (SD).

Data on questionnaire-based demographic and baseline clinical characteristics was missing for n = 4 in the oxytocin group and n = 3 in the placebo group. In addition, information on lifetime posttraumatic stress disorder was missing for n = 1 in the oxytocin group and n = 1 in the placebo group. Furthermore, not all participants completed their diary regarding nasal spray administration (oxytocin: n = 12; placebo: n = 5) and subjective allocation awareness (oxytocin: n = 18; placebo: n = 14). Three participants did not complete follow-up self-report questionnaires on mental health care use while completing the in-person assessments (oxytocin: n = 3; placebo: n = 0).

CAPS, Clinician-Administered PTSD Scale; ETI, Early Trauma Inventory; HADS, Hospital Anxiety and Depression Scale; IES-R, Impact of Events Scale-Revised; PDEQ, Peritraumatic Dissociative Experiences Questionnaire; PDI, Peritraumatic Distress Inventory; PSS, Perceived Stress Scale; T, time; TSQ, Trauma Screening Questionnaire.

[a]Independent t test.

[b]χ^2 test.

[c]Fisher's exact test.

[d]Mann-Whitney U test.

(fixed effect, symptom change from T4–T6) were assessed. Analyses were repeated in completers only (administered ≥13 sprays; n = 79).

Subsequently, using linear mixed modeling we assessed whether the intervention's effect on CAPS scores was moderated by factors in the following domains: 1) participant

characteristics (sex, childhood trauma); 2) peritraumatic and immediate posttraumatic distress (PDI, Peritraumatic Dissociation Experience Questionnaire, and TSQ); and 3) acute symptom severity (baseline CAPS total score).

Following the data-analytic approach of Fournier *et al.* (54), we conducted a stepwise approach for each domain separately. This approach maximizes moderator identification while maintaining an acceptable likelihood of chance capitalization, thus balancing risk for type I and type II errors. In step 1, we added all main and interaction effects for each predictor to the simple linear mixed model. In subsequent steps, effects with p values of $<.20$, $<.10$, and $<.05$, respectively, were retained. Nonsignificant main effects were retained if the corresponding interaction with intervention was above the p value threshold. Continuous predictors were converted to Z scores, and dichotomous predictors were recoded into –0.5 and 0.5 (55). A cutoff of 45 for baseline CAPS total score (56) was used to divide participants into two groups, representing low and high acute PTSD symptom severity (see Supplemental Figure S1 for the distribution of baseline CAPS scores). Bonferroni-corrected post hoc pairwise comparisons of estimated means by the linear mixed model including these two groups were performed to test whether intervention effects were significant within participants with high and low acute PTSD symptom severity, respectively.

Next, linear mixed models were repeated to investigate overall intervention effects for self-reported PTSD, anxiety, and depression and to investigate whether the intervention's effect depended on baseline symptom severity.

In all final models, $p < .05$ was considered statistically significant. Cohen's d was calculated to determine the effect size of differences between oxytocin and placebo groups in outcome measures across follow-up for primary, secondary, and exploratory analyses.

RESULTS

Participant Flow

The study inclusion flowchart is shown in Supplemental Figure S2. In total, 726 screened ED patients scored above TSQ or PDI cutoffs and were therefore considered eligible because of increased PTSD risk. Of these, 152 (20.93%) provided informed consent and completed the baseline assessment to further assess eligibility. These participants had significantly higher TSQ scores than nonparticipants, without significant differences in PDI scores and trauma type (Supplemental Table S1).

We randomized 120 participants, of whom 110 participants received the allocated nasal spray. An additional 3 participants were removed from intention-to-treat analyses because of the later emergence of exclusion criteria ($n = 2$) or having never initiated the intervention ($n = 1$). Thus, the intention-to-treat analyses included 107 participants applying ≥1 dose of the intervention (oxytocin: $n = 53$; placebo: $n = 54$).

Baseline and Trial Characteristics

We observed no significant group differences in demographic, trauma and screening, or baseline clinical characteristics. In addition, there were no significant group differences in subjective intervention allocation awareness, use of mental health care or psychopharmaceuticals (Table 1), or reported adverse events during the trial (Supplemental Table S2). The percentage of dropouts after intervention initiation did not significantly differ between conditions, but participants receiving oxytocin reported having administered significantly more intranasal doses than those receiving placebo (Mann-Whitney U: 742.00, $p = .017$).

Primary Outcome

A preplanned interim analysis of CAPS total score at 1.5 months posttrauma was performed after 50% of the planned sample had received their allocated nasal spray. There was no significant difference in CAPS total score at 1.5 months posttrauma between oxytocin ($n = 43$, mean [SD]: 25.84 [22.97]) and placebo ($n = 48$, mean [SD]: 27.44 [22.03]; square root transformed mean difference [SE]: 0.23 [0.45], $t_{89} = 0.509$, $p = .612$, 95% confidence interval: –0.67 to 1.13, Cohen's $d = 0.107$). As the conditional power to detect a statistically significant difference within the total planned sample ($n = 220$) was $<.20$, recruitment was halted and all follow-up assessments were completed before secondary and exploratory analyses were performed.

Secondary and Exploratory Outcomes

Clinician-Rated PTSD Symptoms. CAPS total scores significantly decreased from 1.5 to 6 months posttrauma (B [SE]: –0.35 [0.05], $t = –7.175$, $p < .001$), without significant group differences in overall symptom severity and symptom decrease over time (effect on intercept [T4]: B [SE]: –0.30 [0.37], $t = –0.826$, $p = .409$; effect on linear slope: B [SE]: 0.04 [0.07], $t = 0.504$, $p = .614$; Cohen's $d = 0.133$; Table 2). Analyses in completers only (oxytocin: $n = 39$, placebo: $n = 40$) showed comparable results (Table 2).

Subsequently it was investigated whether intervention effects were moderated by participant characteristics; peritraumatic and immediate posttraumatic distress measured at T0; and baseline symptom severity measured at T1, before the start of the intervention at T2. Baseline CAPS total score was a significant moderator of intervention effect on follow-up CAPS total scores (CAPS baseline × intervention on intercept: B [SE]: –0.73 [0.30], $t = –2.389$, $p = .017$; Table 3). Post hoc tests showed that oxytocin administration resulted in lower CAPS follow-up scores than placebo for participants with baseline CAPS total scores ≥45 ($F_{1,106} = 8.212$, $p = .006$, Cohen's $d = 0.864$), but not for participants with baseline CAPS total scores <45 ($F_{1,106} = 0.822$, $p = .367$, Cohen's $d = −0.221$; Figure 2). We observed no other significant moderators of intervention effects on CAPS total scores (Table 3).

Self-reported PTSD and Anxiety and Depression Symptoms. IES-R, HADS-anxiety, and HADS-depression scores at follow-up also significantly decreased over time, without significant group differences in overall symptom severity or symptom decrease over time (Cohen's d = IES-R, 0.195; HADS-anxiety, 0.207; HADS-depression, 0.113; Table 2). Baseline IES-R, HADS-anxiety, and

Table 2. Overall Intervention Effects on Clinician-Rated PTSD Symptoms in Intention-to-Treat and Completer Analyses, and on Self-reported PTSD, Depression, and Anxiety Symptoms in Intention-to-Treat Analyses

	Oxytocin (n = 53)	Placebo (n = 54)	Intervention Effect on Intercept				Linear Slope				Intervention × Slope			
	Mean (SD)	Mean (SD)	*B* (SE)	*t* Value	*p* Value	95% CI	*B* (SE)	*t* Value	*p* Value	95% CI	*B* (SE)	*t* Value	*p* Value	95% CI
CAPS (ITT)			−0.30 (0.37)	−0.826	.409	−1.02 to 0.42	−0.35 (0.05)	−7.175	<.001	−0.44 to 0.26	0.04 (0.07)	0.504	.614	−0.10 to 0.17
1.5 months	26.10 (20.83)	27.39 (20.87)												
3 months	16.97 (16.22)	21.24 (18.43)												
6 months	12.78 (12.69)	13.78 (1.77)												
CAPS (Completers)[a]			−0.48 (0.46)	−1.039	.299	−1.38 to 0.42	−0.39 (0.06)	−6.674	.001	−0.51 to 0.28	0.08 (0.08)	1.000	.317	−0.08 to 0.25
1.5 months	25.67 (23.40)	27.98 (23.23)												
3 months	17.05 (18.44)	21.92 (20.04)												
6 months	12.89 (14.36)	12.24 (10.93)												
IES-R			−0.45 (0.35)	−1.305	.192	−1.13 to 0.23	−0.22 (0.05)	−4.571	<.001	−0.32 to −0.13	0.07 (0.07)	0.942	.346	−0.07 to 0.20
1.5 months	18.44 (14.27)	22.83 (17.39)												
3 months	10.27 (10.81)	13.05 (13.58)												
6 months	12.49 (12.91)	12.60 (11.20)												
HADS-Depression			−0.22 (0.24)	−0.914	.361	−0.68 to 0.25	−0.08 (0.03)	−2.352	.019	−0.15 to −0.01	−0.01 (0.05)	−0.127	.899	−0.11 to 0.09
1.5 months	4.77 (4.80)	5.50 (4.64)												
3 months	4.03 (5.50)	4.59 (4.88)												
6 months	3.21 (4.45)	3.92 (4.35)												
HADS-Anxiety			−0.01 (0.21)	−0.045	.964	−0.41 to 0.40	−0.07 (0.03)	−2.205	.028	−0.13 to −0.01	−0.05 (0.05)	−1.066	.287	−0.14 to 0.04
1.5 months	6.27 (4.43)	6.50 (4.38)												
3 months	4.78 (5.04)	5.09 (4.35)												
6 months	4.11 (4.03)	4.88 (4.03)												

Scores are presented as mean and standard deviations, which are pooled estimates obtained from 40 datasets generated using multiple imputation in the intention-to-treat sample of n = 107 participants (number of participants for whom data was imputed: T4: CAPS: n = 16, self-report questionnaires: n = 21; T5: CAPS: n = 22, self-report questionnaires: n = 31; T6: CAPS: n = 23, self-report questionnaires: n = 31). For interpretation of results, presented values represent untransformed scores. Results from statistical analyses represent pooled B (SE), *t*, and *p* values and 95% confidence intervals (CIs) of B obtained from linear mixed models on these 40 imputed datasets, using square root transformed data because of nonnormality of the raw data.

CAPS, Clinician-Administered PTSD Scale; HADS, Hospital Anxiety and Depression Scale; IES-R, Impact of Events Scale-Revised; ITT, intention-to-treat; PTSD, posttraumatic stress disorder.

[a]For CAPS (completers): oxytocin: n = 39, placebo: n = 40.

Table 3. Moderator Analyses on Oxytocin Effects on Clinician-Rated PTSD Symptom Severity at Follow-up Assessments 1.5, 3, and 6 Months Posttrauma

	Intercept				Linear Slope			
	B	SE	*p* Value	95% CI	*B*	SE	*p* Value	95% CI
Domain: Participant Characteristics								
Step 1								
Sex	0.36	0.52	.692	−0.65 to 1.37	−0.07	0.10	.462	−0.27 to 1.21
Childhood trauma (ETI)	−0.12	0.26	.635	−0.64 to 0.39	0.03	0.05	.601	−0.07 to 0.13
Sex × intervention	−0.17	0.74	.822	−1.61 to 1.28	−0.06	0.14	.662	−0.34 to 0.21
Childhood trauma × intervention	0.50	0.37	.178	−0.23 to 1.23	−0.06	0.07	.371	−0.20 to 0.08
Step 2[a]								
Childhood trauma	−0.08	0.24	.732	−0.55 to 0.39				
Childhood trauma × intervention	0.39	0.34	.256	−0.28 to 1.05				
Domain: Peritraumatic and Immediate Posttraumatic Distress								
Step 1								
Distress (PDI)	0.80	0.26	.002	0.29 to 1.31	−0.06	0.05	.230	−0.17 to 0.04
Dissociation (PDEQ)	0.60	0.29	.042	0.02 to 1.17	−0.07	0.06	.267	−0.19 to 0.05
Acute PTSD (TSQ)	0.20	0.24	.411	−0.27 to 0.66	0.02	0.05	.639	−0.07 to 0.12
Distress × intervention	−0.49	0.38	.200	−1.24 to 0.26	0.01	0.08	.915	−0.15 to 0.16
Dissociation × intervention	−0.32	0.37	.388	−1.05 to 0.41	0.07	0.08	.267	−0.09 to 0.22
Acute PTSD × intervention	−0.07	0.36	.842	−0.77 to 0.63	−0.05	0.07	.460	−0.20 to 0.09
Domain: Acute Symptom Severity								
Step 1								
Baseline CAPS score	1.25	0.21	<.001	0.84 to 1.66	−0.08	0.04	.082	−0.16 to 0.01
Baseline CAPS score × intervention	−0.65	0.33	.052	−1.30 to 0.00	−0.04	0.07	.600	−0.17 to 0.10
Steps 2, 3, and 4[b]								
Baseline CAPS score	1.28	0.20	<.001	0.89 to 1.68	−0.09	0.03	.009	−0.16 to −0.02
Baseline CAPS score × intervention	−0.73	0.30	.017	−1.31 to −0.13				

Results represent pooled B (SE), *p* values, and 95% confidence intervals (CIs) of B obtained from linear mixed models on 40 imputed datasets, using square root transformed data because of nonnormality of the raw data (number of participants for whom data was imputed for the CAPS: T4: $n = 16$; T5: $n = 22$; T6: $n = 23$). Stepwise moderator analyses were performed for each domain separately.

CAPS, Clinician-Administered PTSD scale; ETI, Early Trauma Inventory; PDEQ, Peritraumatic Dissociation Experience Questionnaire; PDI, Peritraumatic Distress Inventory; PTSD, posttraumatic stress disorder; TSQ, Trauma Screening Questionnaire.

[a]Retain interaction effects at $p < .20$ and main effects of variables included in retained interaction effects.

[b]Retain interaction effects at $p < .20$, $p < .10$, $p < .05$, respectively, and main effects of variables included in retained interaction effects.

HADS-depression scores did not significantly moderate intervention effects on the respective outcomes at follow-up (Supplemental Table S3). However, exploratory pairwise comparisons within participants with baseline CAPS scores ≥45 revealed that participants receiving oxytocin also had significantly lower IES-R ($F_{1,107} = 8.181$, $p = .005$, Cohen's $d = 0.869$) HADS-depression ($F_{1,107} = 7.180$, $p = .014$, Cohen's $d = 0.752$), and HADS-anxiety ($F_{1,106} = 4.982$, $p = .038$, Cohen's $d = 0.623$) scores across follow-up than participants receiving placebo.

DISCUSSION

In this placebo-controlled trial, we investigated for the first time whether oxytocin administration early after trauma attenuated subsequent clinician-rated PTSD symptom severity in ED patients with acute distress. In all participants, oxytocin administration did not result in significantly lower clinician-rated PTSD symptom severity compared to placebo at 1.5 months posttrauma (our primary outcome) or across follow-up. However, secondary moderator analyses showed an effect of oxytocin dependent on acute PTSD symptom severity, as assessed at baseline within 10 days posttrauma. Relative to placebo-treated individuals with high acute PTSD symptoms, oxytocin-treated participants with high acute PTSD symptoms had significantly lower PTSD symptom severity across the complete follow-up period up to 6 months posttrauma, indicating a long-term protective effect. In addition, exploratory analyses showed that these participants also had lower self-reported PTSD, depression, and anxiety symptom severity across follow-up. Oxytocin administration had no effect on follow-up PTSD symptoms for individuals with relatively low acute PTSD symptom severity. Although our findings result from secondary and exploratory analyses and warrant replication, they indicate that intranasal oxytocin administration is a promising preventive intervention for PTSD for individuals with high acute PTSD symptoms. We also carefully assessed adverse events throughout the trial. We observed no differences in adverse event frequency between interventions, suggesting that oxytocin administration early after trauma is well tolerated.

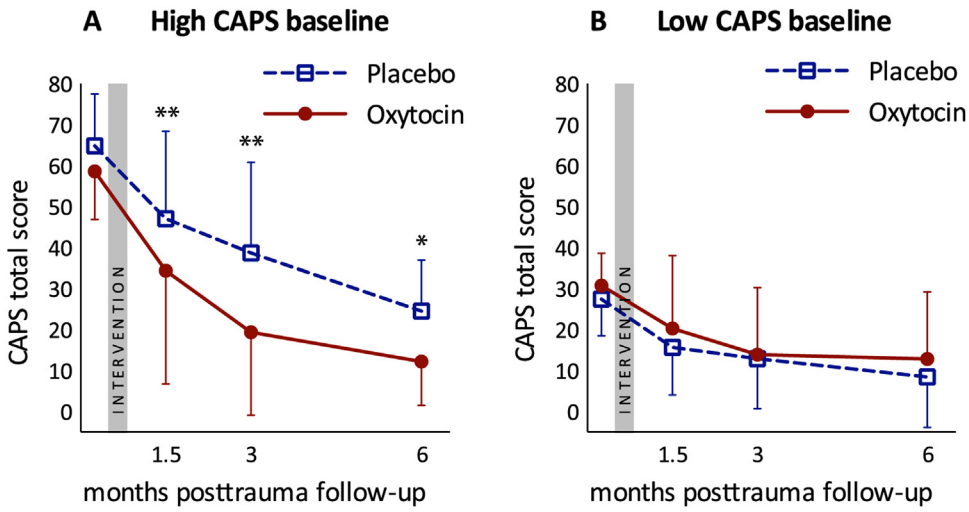

Figure 2. Moderator effect of acute clinician-rated posttraumatic stress disorder (PTSD) symptom severity on the effect of oxytocin administration on clinician-rated PTSD symptom severity at follow-up. **(A)** Participants with baseline Clinician-Administered PTSD Scale (CAPS) total scores ≥45 receiving oxytocin had significantly lower CAPS total scores across follow-up than participants with baseline CAPS total scores ≥45 receiving placebo ($F_{1,106} = 8.212$, $p = .006$ Bonferroni-corrected), with post hoc pairwise comparisons showing significant differences at each follow-up assessment (*$p < .05$, **$p < .01$, Bonferroni-corrected). **(B)** CAPS total scores across follow-up did not significantly differ between participants with baseline CAPS total scores <45 receiving oxytocin and placebo ($F_{1,106} = 0.822$, $p = .367$). Data are presented as nonimputed, nontransformed means ± SD.

Six serious adverse events were reported during the trial, of which five consisted of preplanned surgeries related to injuries sustained during the recent traumatic event. Notably, the need for effective and safe PTSD prevention is longstanding and ongoing, with no preventive interventions currently at the stage of widespread implementation (57). Previously, hydrocortisone (4,5) and prolonged exposure (3) initiated within 12 hours posttrauma in ED patients, and brief cognitive behavioral therapy within the first weeks posttrauma in patients with acute stress disorder (6), were found to reduce subsequent PTSD symptom severity. The feasibility, acceptability, and tolerability of preventive interventions may differ across settings and individuals, and it is preferable to have multiple evidence-based interventions available varying in type (pharmacological vs. psychological) and timing. The current randomized controlled trial is the first to show efficacy of a pharmacological agent other than hydrocortisone in reducing PTSD symptom development (58,59). In addition, the oxytocin intervention was initiated within approximately 2 weeks posttrauma, and therefore it is also of interest for use in ED patients for whom immediate intervention is not feasible or in traumatized populations that are not immediately brought to the attention of health care professionals.

Individuals with high acute PTSD symptoms are at increased risk to subsequently be diagnosed with PTSD (60,61). Therefore, our finding of beneficial effects specifically in individuals with high acute PTSD symptoms adds to the growing recognition that selective prevention based upon individual risk estimation is more effective than nonselective prevention (62). All previous findings of effective PTSD prevention were observed in participants with increased risk for PTSD [i.e., caused by perceived life-threat (3), peritraumatic dissociation (4), or subthreshold acute stress disorder (5,6)]. In addition, an online cognitive behavioral therapy–based intervention only reduced PTSD symptoms in participants with high acute PTSD symptoms (63). Also, selective prevention may diminish the risk for interference with adaptive recovery, as was previously observed for debriefing (62).

Furthermore, the observation that oxytocin administration had differential effects dependent on acute PTSD symptom severity adds to a growing body of literature indicating that the presence and severity of psychiatric symptoms moderates central and peripheral effects of oxytocin administration (16,64). Intranasal oxytocin seems to only exert beneficial effects in individuals with suboptimal functioning in domains affected by oxytocin (16,32,65), although a solid neurobiological basis for this hypothesis is still lacking.

We hypothesized intranasal oxytocin to be a promising preventive strategy for PTSD given previously observed effects of oxytocin administration on neuroendocrine and physiological stress reactivity, anxiety, neural fear and threat processing, and socioemotional functioning, which all have been associated with vulnerability for PTSD (16–21). Also, functioning of the oxytocin system itself may be related to PTSD vulnerability (66,67). Our exploratory finding that oxytocin attenuated self-reported anxiety symptoms in individuals with high acute PTSD symptoms suggests that anxiolytic effects may underlie the observed effects on PTSD symptomatology. However, the exact mechanisms underlying our observed effects of oxytocin in individuals with high acute PTSD symptoms cannot be inferred from these clinical data. To gain a mechanistic understanding of our findings, future research should assess whether repeated oxytocin administration early after trauma affects neurobiological and socioemotional processes as well as functioning of the oxytocin system itself. Furthermore, it should be investigated whether these factors are associated with the observed differential effects of oxytocin administration dependent on acute PTSD symptom severity.

This study is the largest published clinical randomized controlled trial on effects of intranasal oxytocin on psychiatric symptoms to date. Furthermore, to the best of our knowledge, this is the first randomized controlled trial assessing whether sex, trauma history, and baseline symptom severity moderate the effects of repeated oxytocin administration. In addition, our in-person follow-up up to 6 months posttrauma enabled us to

demonstrate that oxytocin's effects on clinician-rated PTSD were sustained for a significant period of time.

However, some limitations need to be addressed. As the interim analysis at 50% of planned inclusion indicated low conditional power to detect a significant effect of oxytocin on clinician-rated PTSD symptom severity at study completion, we halted inclusion. Consequently, our sample size was modest, and replicating our findings is important.

In addition, although moderate to severe distress during or immediately after trauma was an inclusion criterion for our study, there was considerable variability in baseline CAPS scores within 10 days posttrauma: only 40.2% of the participants scored above a previously established severity threshold optimally sensitive for PTSD [CAPS $\geq$ 45 (56)]. Furthermore, in both treatment groups we observed a steady decrease in PTSD symptom severity over time: the percentage of participants screening positive for PTSD declined from 19.8% at 1.5 months posttrauma to 6.0% at 6 months posttrauma. Thus, our screeners for peritraumatic and immediate posttraumatic distress may have had lower specificity for PTSD than previously reported. This may be because our screening questionnaires were administered earlier after trauma than in previous validation studies. Moreover, we adapted the TSQ to accommodate the short time window between the traumatic event and screening [i.e., requiring symptoms to have occurred at least once instead of twice (41)]. Therefore, we may have included more participants with relatively low PTSD risk than anticipated, potentially also explaining why we found a differential intervention effect dependent on clinician-rated acute PTSD severity instead of the hypothesized overall intervention effect. On the other hand, despite the relatively few participants screening positive for PTSD at the final assessment, 23% of participants reported mental health care use during the follow-up period. This may indicate that participating in this trial stimulated participants to seek professional help relatively early, which could be an alternative explanation for the observed steady decrease in symptom severity.

Also, because >80% of our participants visited the ED because of accidents, we could not investigate whether trauma type moderated oxytocin effects. Rothbaum *et al.* (3) observed that rape victims benefitted most from early prolonged exposure compared to ED patients with other types of trauma exposure. Furthermore, in rodents, central oxytocin administration before conditioned fear extinction improved social fear extinction (68) but impaired nonsocial fear extinction (69). Such differential oxytocin administration effects on PTSD development dependent on the social or interpersonal nature of the trauma would have important implications for generalization of our findings. Finally, we did not investigate whether a different timing, dosage, or duration of oxytocin administration would also be effective in reducing subsequent PTSD symptom severity. There is ongoing debate on pharmacodynamics of intranasal oxytocin administration (70–73). We acknowledge that this is an important research avenue and that future clinical studies on oxytocin administration would greatly benefit from increased knowledge on these fundamental issues.

In conclusion, repeated intranasal oxytocin administration initiated early after trauma did not attenuate clinician-rated PTSD symptom severity in all recently trauma-exposed individuals with acute distress. However, participants with high acute PTSD symptoms receiving oxytocin showed significantly lower PTSD symptom severity across follow-up compared to placebo. Although replication is necessary, our findings indicate that intranasal oxytocin administration is a promising novel preventive intervention for individuals at increased risk for PTSD because of high acute symptom severity.

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Netherlands Trial Registry: Boosting Oxytocin After Trauma; http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=3190; NTR3190.

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