Archival Report

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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

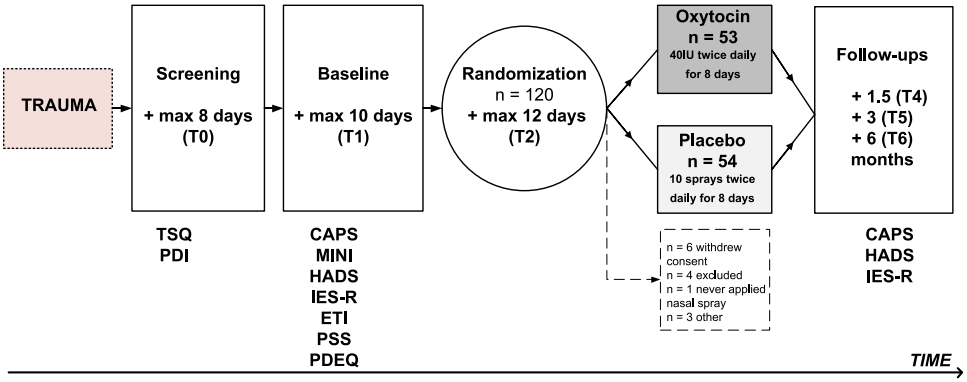

Figure 1. Overview of the study design. CAPS, Clinician-Administered PTSD Scale; ETI, Early Trauma Inventory; HADS, Hospital Anxiety and Depression Scale; IES-R, Impact of Events Scale-Revised; MINI, Mini-International Neuropsychiatric Interview; PDEQ, Peritraumatic Dissociative Experiences Questionnaire;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