This is the author preprint. After peer review the paper has been published in *Psychopharmacology (2018), 235*, 8, 2471-2477. DOI:10.1007/s00213-018-4945-1

No side-effects of single intranasal oxytocin administration in middle childhood

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Keywords: Oxytocin, Side-effects, Middle childhood, Randomized controlled trial, Intranasal administration

Acknowledgments: This work was supported by grants G.0774.15 and G.0757.18N from Research Foundation Flanders (FWO) and CREA/12/004 from Research Fund KU Leuven. MJBK was supported by an Advanced Grant from the European Research Council. The authors declare that they have no competing interests.

Abstract

Despite growing interest in the (therapeutic) use of intranasal oxytocin administration in children, the potential side-effects of intranasal oxytocin have remained largely unclear to date. The current study is the first double-blind randomized controlled trial to examine side-effects following single administration of oxytocin nasal spray in elementary school-aged children. One hundred children (8-12 years old) were randomly assigned to receive oxytocin or placebo nasal spray. We assessed side-effects by means of a standardized, drug-specific questionnaire and an open-ended question at two time points: 90 minutes after nasal spray administration and 24 hours after administration. Results showed that there were no significant associations between nasal spray condition and total frequency of reported side-effects or reports of specific side-effects. Children and their mothers were unable to correctly guess nasal spray allocation, further supporting that the subjective experience of oxytocin versus placebo nasal spray effects was similar. Moreover, the majority of reported side-effects were classified as mild and ceased within 24 hours after the procedure, indicating that the nasal sprays were well-tolerated. In all, this study is the first randomized controlled trial to provide information on the safety of intranasal oxytocin administration in middle childhood. The current study suggests that single administration of intranasal oxytocin is likely safe in elementary school-age children.

Research with intranasal oxytocin administration is a growing field, extending to research with children. The beneficial social effects of oxytocin have generated interest in the therapeutic potential of intranasal oxytocin for mental health disorders characterized by impairments in social functioning. When considering oxytocin as a treatment option, however, it is crucial to examine not only efficacy but also safety of oxytocin administration. Therefore, several scholars have expressed the need for assessment of safety and side-effects of intranasal oxytocin, particularly in children (Liu et al. 2012; Miller 2013; Van IJzendoorn and Bakermans-Kranenburg 2016).

A review of the safety of intranasal oxytocin in humans indicated no clear association between oxytocin administration and side-effects (MacDonald et al. 2011), however, this review only included one trial with a child sample. A more recent review focused on oxytocin safety and side-effects in pediatric samples (DeMayo et al. 2017). Out of seven randomized controlled trials that reported information about side-effects (total $n = 214$), two reported (a trend toward) adverse events following intranasal oxytocin (Einfeld et al. 2014; Yatawara et al. 2016). In the remaining five trials, no side-effects were found (DeMayo et al. 2017). However, sample sizes of these trials were small and differences in outcome measures and methods prohibit combining the data to allow for a more reliable examination of potential side-effects. Moreover, no studies have looked at side-effects of oxytocin in a general population sample. As a result, to date the potential side-effects of intranasal oxytocin administration in children have remained largely unclear.

The current study is the first double-blind randomized controlled trial to examine side-effects following single administration of oxytocin nasal spray in a relatively large ($n = 100$), general population middle childhood sample. To this aim, we (1) tested associations between nasal spray condition (oxytocin versus placebo) and total frequency of reported side-effects as well as incidence of specific side-effects; (2) explored whether gender and age of the participants were moderators of the association between nasal spray condition and reported side-effects; (3) assessed if children and mothers were able to correctly guess nasal spray allocation and whether their subjective perception of nasal spray condition was associated with reported side-effects.

Methods

Procedure

Participants were recruited via the distribution of flyers. Demographic information of the participants is reported in Table 1. Inclusion criteria were: 8-12 years old, able to comprehend and read the Dutch language. Exclusion criteria were: known oxytocin allergy, current medication use, a kidney or cardiac condition. One hundred fifty-four parent-child dyads stated interest in the study, of which 64.9% participated (see Figure 1 for a flowchart). Mothers were asked to make sure that children abstained from caffeine for at least two hours before study onset. Upon arrival at the laboratory, mother and child completed written informed consent and assent respectively. As part of a larger study on the effects of oxytocin combined with a cognitive bias modification training, children participated in one of two computerized trainings and completed measures of trust in maternal support (Verhees et al., 2017). Side-effects were assessed at two time points: at the end of the procedure (T1; on average around 90 minutes after nasal spray administration) side-effects were assessed by means of a child questionnaire; 24 hours after the procedure (T2) mothers were asked the same questions via phone, assessing the occurrence of side-effects since they left the laboratory (see below for more details).

Study design

The study was a double-blind randomized controlled trial, with 50 participants in the oxytocin condition and 50 participants in the placebo condition. Randomization of the nasal sprays was performed as permuted block randomization (Doig and Simpson 2005) at the University Hospital of Heidelberg, Germany, and was stratified by computerized training condition. The nasal sprays were numbered and for each nasal spray number a sealed envelope contained a piece of paper linking the spray number to one of the nasal spray conditions. We assigned the nasal sprays to consecutive participants in sequential order (with training condition alternated between participants). Participants and experimenters were blind to nasal spray condition and blinding was maintained until data collection was finished. The study took place at the Parenting and Special Education Research Unit KU Leuven, Belgium between March and November 2016. The Medical Ethics Committee UZ KU Leuven/Research approved the study. The trial was registered in the database of ClinicalTrials.gov

(NCT02737254). Full details of the study design and procedure are available in the published study protocol (Verhees et al. 2017).

Nasal spray

Children in the oxytocin condition received a nasal spray containing oxytocin (in a concentration of 40 international units(IU)/ml), children in the placebo condition received a nasal spray containing 0.9% sodium-chloride solution. Following prior oxytocin research in child samples (Dadds et al. 2014), the amount of nasal spray administered was based on the child's weight: children under 40 kg administered 0.3 ml nasal spray (i.e. 12 IU oxytocin for the oxytocin condition), children over 40 kg administered 0.6 ml nasal spray (i.e. 24 IU oxytocin for the oxytocin condition). The nasal spray administration procedure was based on recommendations by Guastella et al. (2013). First the nasal spray was primed until a fine mist was visibly released, after which we weighed the nasal spray bottle on an apothecary scale (Kern EMB 200-2). Either the experimenter or the child, under experimenter supervision, administered the nasal spray. Child and experimenter practiced the administration procedure before actual administration. Children kept their head upright or slightly tilted backwards during administration. Administration was alternated between nostrils. The child kept the other nostril closed with one finger, and inhaled lightly two or three times upon nasal spray delivery. Experimenters made sure that the top of the nasal spray was inserted about 1 cm into the nose and that the bottle was held at a slight angle such that the pipe was well immersed in the fluid. After 6 versus 12 pumps (for children under versus over 40 kg) we weighed the nasal spray bottle again and if necessary administered extra pumps. There were no differences between nasal spray conditions in distribution of gender ($\chi^2(1) = 0.64$, $p = .55$) and age ($t(98) = 1.31$, $p = .19$).

Side-effects assessment

Following recommendations by Greenhill et al. (2003), we administered a standardized, drug-specific questionnaire for the assessment of side-effects. Specifically, we used a checklist comprising 10 different subjectively experienced effects of oxytocin that were most commonly reported across 38 randomized controlled trials (MacDonald et al. 2011), i.e. dizziness, drowsiness, dry throat/mouth,

irritated nose, runny nose, stomach ache, headache, feeling anxious, being very happy and energetic, and feeling relaxed. Additionally, we included an open-ended question inquiring about any other noted changes, allowing the report of any additional experienced effects. In the current article, all these subjective effects are labeled side-effects, however, it must be noted that some effects (e.g. feeling relaxed) could also be considered main effects of oxytocin.

At T1, children were asked for all side-effects whether they experienced it and if so, how severely (mildly, moderately or severely). At this point, children and experimenters also indicated their subjective perception of nasal spray allocation (oxytocin or placebo). At T2, we went through the same checklist and open-ended question with the mothers via phone, assessing whether the side-effects had occurred in the past 24 hours. In addition, we registered onset and duration for every noted side-effect at T2 and mothers indicated their subjective perception of nasal spray allocation.

There was no missing data for the side-effects. To assess associations between nasal spray condition and experienced side-effects, we examined both total number of reported side-effects (minimally mild) as well as incidence of separate side-effects (minimally mild). Severity, onset and duration of side-effects were used for descriptive purposes. For the subjective perception of drug allocation, there was no missing data for children and experimenters. Four mothers indicated they had absolutely no idea which nasal spray their child received: these mothers were left out only of the analyses involving mothers' allocation perception.

Results

Descriptive results

Information about the side-effects reported at T1 by children and at T2 by their mothers in both conditions is presented in Table 2. At T1, 16% of the participants reported no side-effects, while at T2 for 60% no side-effects in the past 24 hours were reported. The majority of side-effects reported was classified as mild (T1: 61.7%; T2: 63.2%). Moreover, 46.1% of reported side-effects at T2 had ceased within 4 hours after onset and 88.2% had cleared 24 hours after the procedure. Since 8% of the mothers reported that their child showed more affectionate behaviour after the procedure, this was included as a separate side-effect. Other spontaneously reported side-effects were mentioned only once

and included pain in the eyes (child-reported), insomnia, hunger, loss of smell, and flu symptoms (mother-reported). There was a positive relationship between total frequency of reported side-effects at T1 and at T2 (r = .30, p < .005). Moreover, we found associations between T1 and T2 reporting of the side-effects Dizziness/light-headedness (p < .005, Fisher's exact test) and Dry throat/mouth (p < .05, Fisher's exact test). No other significant associations between T1 and T2 report of the separate side-effects were found (ps between .05 and 1.00, Fisher's exact test), which might be due to restriction of range because for most side-effects variance drops from T1 to T2.

Associations between side-effects and nasal spray condition

There were no differences between the oxytocin and placebo conditions in total number of side-effects reported at T1: $t(98) = 0.00$, $p = 1.00$, Cohen's $d = 0.00$, or at T2: $t(98) = -0.45$, $p = .65$, $d = -0.09$. For the analyses of the separate side-effects, we corrected for multiple testing (10 tests for child-reported side-effects, 11 tests for mother-reported side-effects) by considering effects for which p–values <.005 as statistically significant. There were no significant associations between nasal spray condition and the separate side-effects reported at T1 (ps between .07 and 1.00, Fisher's exact test) or at T2 (ps between .12 and 1.00, Fisher's exact test). Effect sizes for the associations between nasal spray condition and the separate side-effects can be found in Table 2.

Moderation by gender and age. Gender did not moderate the effect of spray on total number of side-effects reported at T1: $F(1,96) = 3.66$, $p = .06$, $\eta_p^2 = .04$, or at T2: $F(1,96) = 1.44$, $p = .23$, $\eta_p^2 = .02$. Gender moderated the effect of spray on side-effect Runny nose reported at T1 ($\chi^2(1) = 9.27$, $p = .002$, $d = 0.64$), indicating that for boys there was a trend towards more often reporting a runny nose after oxytocin than placebo (p = .05, Fisher's exact test), while this was not the case for girls (p = .15, Fisher's exact test). Gender did not moderate the effects of spray on any other side-effects at T1 (χ^2s between 0.00 and 2.97, ps between .09 and 1.00), or at T2 (χ^2s between 0.00 and 6.19, ps between .01 and 1.00).

Additionally, age did not moderate effects of nasal spray on total frequency of side-effects: T1: $F(1,96) = 0.02$, $p = .88$, $\eta^2 = .00$; T2: $F(1,96) = 3.87$, $p = .05$, $\eta^2 = .04$. Age only moderated the effect of spray on side-effect Dry throat/mouth reported at T2 ($\chi^2(1) = 13.08$, p <.001, $d = 0.78$),

indicating that mothers of older children (+1*SD* from the sample mean age) showed a trend towards more often reporting that their child experienced a dry throat or mouth after oxytocin than placebo ($\chi^2(1) = 3.06$, $p = .08$), while no such effect was found for younger children (-1*SD* from sample mean age: $\chi^2(1) = 0.69$, $p = .41$). Age did not moderate the association between nasal spray condition and any side-effects reported at T1 (χ^2s between 0.03 and 6.72, *p*s between .01 and .87), or any other side-effects reported at T2 (χ^2s between 0.00 and 0.97, *p*s between .33 and 1.00).

Subjective perception of drug allocation

Children ($\chi^2(1) = 0.38$, $p = .68$, $d = 0.12$) and experimenters ($\chi^2(1) = 0.04$, $p = 1.00$, $d = 0.04$) at T1, and mothers ($\chi^2(1) = 2.69$, $p = .14$, $d = 0.34$) at T2 were unable to correctly guess nasal spray allocation. There was no relationship between children's condition perception at T1 and total number of reported side-effects at either time point (T1: $t(98) = -1.25$, $p = .22$, $d = -0.26$; T2: $t(98) = -1.29$, $p = .20$, $d = -0.26$). There were no associations between children's condition perception and separate side-effects reported at T1 (*p*s between .07 and 1.00, Fisher's exact test) or at T2 (*p*s between .02 and 1.00, Fisher's exact test).

There was no relationship between total number of side-effects reported at T1 and mother's condition perception at T2 ($t(94) = -0.45$, $p = .65$, $d = -0.10$). Mothers' condition perception was related to total frequency of reported side-effects at T2 ($t(94) = 3.27$, $p < .003$, $d = 0.78$), with mothers who thought their child received oxytocin reporting more side-effects at T2 ($M = 1.26$, $SD = 1.29$) than mothers who thought their child received placebo ($M = 0.46$, $SD = 0.85$). Moreover, mothers who thought their children received oxytocin indicated more often at T2 that their child was very happy, energetic ($p < .008$, Fisher's exact test). No significant associations between mothers' condition perception and separate side-effects reported at T1 (*p*s between .02 and 1.00, Fisher's exact test), or any other side-effects reported at T2 were found (*p*s between .06 and 1.00, Fisher's exact test).

Discussion

This study was the first to test side-effects following intranasal oxytocin administration in a sample of normally developing, 8 – 12 year-old children. To this aim, we questioned children about

experienced side-effects after intranasal administration of either oxytocin or a placebo at the end of the procedure (T1). Additionally, after 24 hours (T2), their mothers reported on any noted side-effects since they left the laboratory. The results showed that there were no significant associations between nasal spray condition and total frequency of reported side-effects or between nasal spray condition and reports of specific side-effects, both at T1 and T2. Boys more often reported a runny nose after oxytocin than placebo as compared to girls at T1. Additionally, at T2 mothers of older children reported more often that their child experienced a dry mouth or throat after oxytocin than placebo as compared to mothers of younger children. No other effects of gender or age on reported side-effects after oxytocin versus placebo were found. Children, mothers and experimenters were unable to differentiate whether the children had received oxytocin or placebo. Mothers who thought their children received oxytocin reported more side-effects overall and more often reported their child to be very happy and energetic (both at T2).

The current study is the first to report that single administration of 12 IU oxytocin for children under 40 kg and 24 IU oxytocin for children over 40 kg does not result in significantly more adverse or side-effects as compared to placebo. The fact that in the present study neither children, nor mothers, nor experimenters could not correctly guess which nasal spray the child received further supports the claim that the subjective experience of oxytocin versus placebo nasal spray effects was similar. These results are in line with previous reviews, based on smaller pediatric (DeMayo et al. 2017) and adult samples (MacDonald et al. 2011), indicating that intranasal oxytocin does not produce reliable side-effects.

Interestingly, the total frequency of reported side-effects was considerable. That is, across nasal spray conditions, 84% of the children reported at least one side-effect at the end of the procedure, and 40% of the mothers reported at least one side-effect within 24 hours after the procedure. A possible explanation is that expectancy effects following the administration of nasal spray may have caused participants to closely monitor subjective effects and led to an amplified perception of side-effects (Rief et al. 2006). Moreover, we used a targeted, active method, to assess side-effects in the present study. It has been shown that specific and active inquiry yields a higher frequency of reported side-effects than less-targeted or more passive methods of side-effect

monitoring (Loke et al. 2007; MacDonald et al. 2011). Importantly, the finding that side-effects were frequently reported, both after oxytocin and placebo nasal spray, does not necessarily suggest that the nasal sprays were not well-tolerated in the current study. That is, the majority of reported side-effects were classified as mild and ceased within 24 hours after the procedure, indicating that there were no severe adverse events.

As the present study investigated the safety of single administration of intranasal oxytocin in 8-12 year old children, we cannot extrapolate the findings to multiple administration. It is interesting to note here that MacDonald et al. (2011) in their review found that in adults intranasal oxytocin administration over a period of 13 weeks resulted in a similar frequency of reported side-effects as short-term administration. Nonetheless, future research investigating the safety of multiple administration of oxytocin in children, as well as long-term side-effects, is clearly needed. Moreover, children who were possibly more at risk for side-effects were excluded from the current trial (i.e. children with a kidney or cardiac condition or currently using medication). This is important to consider when interpreting the current findings, as we cannot draw conclusions for children who meet these exclusion criteria.

The present study is the first randomized controlled trial to provide information on the safety of intranasal oxytocin administration in a middle childhood sample. As larger-scale trials with children are currently under way and oxytocin is considered for its clinical applicability in child samples, careful consideration of potential side-effects is essential. In the current study, side-effects following oxytocin were not more frequent than side-effects following placebo, and the results suggest that single administration of intranasal oxytocin is likely safe in child samples.

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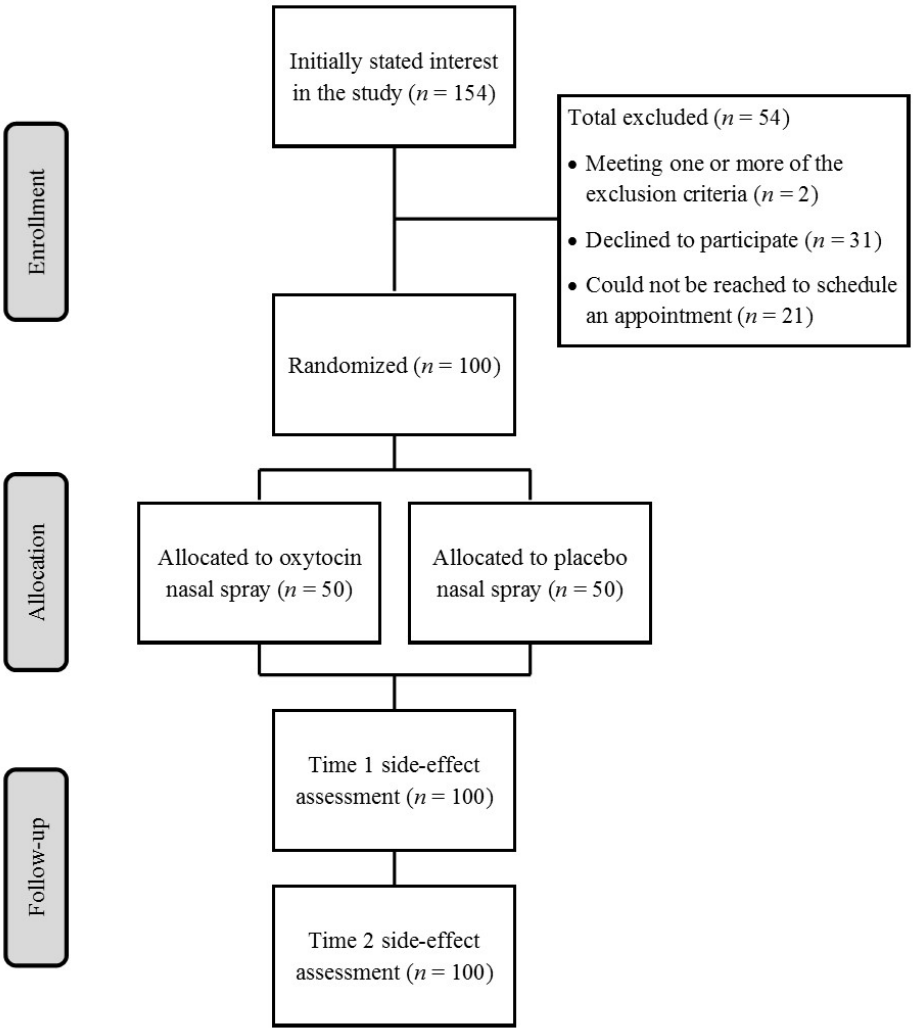

Figure 1. Consort flow diagram.

Table 1. Demographic information of participants per nasal spray condition.

	Oxytocin (n = 50)	Placebo (n = 50)
Gender		
Boy	25 (50%)	21 (42%)
Girl	25 (50%)	29 (58%)
Age, *M* (*SD)*	9.88 (1.19)	10.19 (1.20)
Weight		
< 40 kg	43 (86%)	41 (82%)
> 40 kg	7 (14%)	9 (18%)

Table 2. Reported side-effects at Time 1 and Time 2.

	Time 1							Time 2									
	Frequency			Effect size	Severity			Frequency			Effect size	Severity			Onset	Duration	Symptoms ceased
Side-effect	Total	OT	PL	Cohen's *d*	Mild	Moderate	Severe	Total	OT	PL	Cohen's *d*	Mild	Moderate	Severe	Within 2h	< 4h	Within 24h
Dizziness, light-headedness	12	9	3	0.38	67%	33%		3	3	0	0.36	100%			100%		100%
Drowsiness	30	13	17	0.18	77%	23%		13	7	6	0.06	62%	31%	8%	69%	69%	100%
Dry throat/dry mouth	27	13	14	0.04	67%	33%		8	5	3	0.15	88%	13%		75%	63%	
Nasal irritation	8	4	4	0.00	50%	50%		1	0	1	0.20	100%					100%
Runny nose	14	7	7	0.00	50%	50%		3	1	2	0.12	67%		33%	67%	67%	100%
Stomach ache	5	4	1	0.28	80%	20%		4	0	4	0.42	75%	25%		50%		25%
Anxious, worried, uncomfortable								2	2	0	0.29	50%	50%			100%	100%
Energetic, euphoric, very happy	44	17	27	0.41	57%	34%	9%	12	8	4	0.25	67%	25%	8%	100%	75%	92%
Calm, relaxed, comfortable	46	26	20	0.24	52%	41%	7%	13	7	6	0.06	54%	31%	15%	69%	31%	85%
Headache	9	5	4	0.07	78%	22%		4	2	2	0.00	50%	25%	25%	75%	25%	75%
Affectionate behaviour								8	4	4	0.00	50%	38%	13%	88%	13%	88%
Other[a]	1	0	1		100%			4	2	2		75%		25%	50%	50%	75%

Note. OT = oxytocin condition, PL = placebo condition.

[a]Other side-effects that were only reported once included: pain in the eyes (Time 1), insomnia, hunger, loss of smell and flu symptoms (Time 2).