RESEARCH LETTER

Effect of Oxytocin on Placebo Analgesia: A Randomized Study

Placebo responses have been shown to contribute to clinical treatment outcomes. The pharmacological enhancement of placebo responses therefore has the potential to increase treatment benefits. The neuropeptide oxytocin may mediate processes such as empathy, trust, and social learning. These are key elements of the patient-physician relationship, which is an important mediator of placebo responses. We tested whether oxytocin enhances the placebo response in an experimental placebo analgesia model.

Methods | In January to September 2012, we recruited 80 healthy male volunteers at the University of Hamburg, Germany. Based on previous data, we expected this sample size to provide 80% power to detect an effect size of 0.35 with a 2-sided α of .05. Participants were randomly assigned to the double-blind administration of 40 IU of oxytocin or saline intranasally using a simple algorithm. After 45 minutes, placebo analgesia was assessed using an established paradigm. Two identical inert ointments were applied to 2 sites on each participant’s forearm, with the sites randomized across participants. The ointments were introduced by a male study physician using a script, described as an anesthetic that reduces pain (placebo) and an inert control cream (control). During the 15 minutes in which the anesthetic was believed to take effect, a calibration procedure was performed to identify the individual stimulation intensity at which a 20-second painful heat stimulus (Medoc-TSA-II; NeuroSensory Analyser) was perceived as a 60 on a visual analogue scale (VAS) (ranging from 0, no pain, to 100, unbearable pain). During the subsequent test phase, a series of 10 stimuli of the calibrated intensity was applied to each of the 2 sites in pseudorandomized order. Each stimulus lasted for 20 seconds, followed by a rating procedure and 40-second rest.

The primary outcome was the placebo analgesic response, defined as the reduction of perceived pain intensity on the placebo site compared with the control site in the oxytocin and saline groups. We also assessed the temperatures needed to induce a sensation of VAS score 60, physical and psychological adverse effects (using the multidimensional mood scale and an open response format), and participants’ treatment guess, to control for an effect of oxytocin on general pain sensitivity and blinding. Measures were analyzed using repeated-measures analysis of variance, 2-tailed 2-sample t tests, or χ² test. Statistical threshold was set at P < .05. Statistical analyses were performed using PASW Statistics version 18.0 (IBM SPSS). The study was approved by the local ethics committee, and all participants provided written informed consent.

Results | Data for 5 participants were excluded because of technical failure, leaving 75 participants (age, 20–38 years; oxytocin group, n = 37). Groups did not differ significantly with regard to age, weight, anxiety, or depression scores (Table 1). Despite identical thermal stimulation on both sites, pain ratings for the placebo site were significantly lower compared with the control site across both treatment groups (Table 2). The placebo analgesic response was significantly higher in the oxytocin group compared with the saline group (oxytocin group difference, 12.84 [95% CI, 8.67-17.01]; saline group difference, 7.08 [95% CI, 3.84-10.31]) (Table 2). Temperature levels needed to induce a sensation of VAS score 60, pain ratings on the control site, adverse effects, and post hoc treatment guesses did not differ significantly between groups (Table 2), consistent with oxytocin having no analgesic effect. The dose of oxytocin induced no significant adverse effects.

Discussion | To our knowledge, our study provides the first experimental evidence that placebo responses can be pharmacologically enhanced by the application of intranasal oxytocin. This effect was not explained by a general effect

Table 1. Participants’ Characteristics

<table>
<thead>
<tr>
<th>Mean (95% CI)</th>
<th>Overall</th>
<th>t Result</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oxytocin Group</strong></td>
<td><strong>Saline Group</strong></td>
<td><strong>t</strong></td>
<td><strong>P Value</strong></td>
</tr>
<tr>
<td>Age, y</td>
<td>26.2 (24.9-27.6)</td>
<td>26.1 (24.7-27.5)</td>
<td>26.2 (25.3-27.1)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>80.4 (76.6-84.2)</td>
<td>81.8 (77.7-85.8)</td>
<td>81.1 (78.4-83.8)</td>
</tr>
<tr>
<td>Anxiety score&lt;sup&gt;®&lt;/sup&gt;</td>
<td>33.9 (30.9-37.0)</td>
<td>35.2 (33.6-36.8)</td>
<td>34.6 (32.9-36.3)</td>
</tr>
<tr>
<td>Depression score&lt;sup&gt;®&lt;/sup&gt;</td>
<td>6.0 (4.3-7.7)</td>
<td>8.1 (5.7-10.6)</td>
<td>7.1 (5.6-8.6)</td>
</tr>
</tbody>
</table>

<sup>®</sup> Participants’ characteristics were compared between groups using 2-tailed 2-sample t tests. Groups did not differ significantly with respect to weight, age, anxiety, and depression score.

<sup>®</sup> Assessed via State-Trait Anxiety Inventory (STAI).<sup>®</sup>
<sup>®</sup> Assessed via General Depression Scale (Allgemeine Depressionsskala [ADS]).
Abbreviation: VAS, visual analogue scale (range, 0-100).

Study concept and design: Data analysis. Mr Kessner and Dr Sprenger contributed equally to this work.

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Author Contributions: Dr Bingel had full access to all of the data obtained in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Mr Kessner and Dr Sprenger contributed equally to this work. Study concept and design: Sprenger, Wiech, Bingel.

Acquisition of data: Kessner, Sprenger.
Analysis and interpretation of data: Kessner, Sprenger, Wrobel, Wiech, Bingel.
Drafting of the manuscript: Kessner, Wiech, Bingel.
Critical revision of the manuscript for important intellectual content: Sprenger, Wrobel, Wiech, Bingel.
Statistical analysis: Kessner, Wrobel.
Obtained funding: Bingel.
Administrative, technical, or material support: Kessner, Sprenger.
Study supervision: Wiech, Bingel.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Bingel reported having received payment from various congresses for reimbursement of travel expenses. Dr Bingel reported having received payments for lectures about pain and placebo responses from Grunenthal and Bayer and having had a consultant contract about placebo and pain with the company Bionorica. No other disclosures were reported.

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Table 2. Primary and Exploratory Outcome Measures

<table>
<thead>
<tr>
<th>Pain rating during test phase, mean (95% CI), VAS score a</th>
<th>Oxytocin Group</th>
<th>Saline Group</th>
<th>Overall Mean Difference</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control site</td>
<td>59.96 (57.28 to 62.64)</td>
<td>58.31 (55.89 to 60.73)</td>
<td>59.12 (57.35 to 60.89)</td>
<td></td>
</tr>
<tr>
<td>Placebo site</td>
<td>47.11 (42.37 to 51.85)</td>
<td>51.23 (47.68 to 54.78)</td>
<td>49.20 (46.28 to 52.12)</td>
<td></td>
</tr>
</tbody>
</table>

Comparison control site:
\[ \chi^2_{1,73} = 7.33, P = .09 \]

Adverse effects (sum score) b

<table>
<thead>
<tr>
<th>Oxytocin Group</th>
<th>Saline Group</th>
<th>Overall Mean Difference</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo response (control – placebo)</td>
<td>12.84 (8.67 to 17.01)</td>
<td>7.08 (3.84 to 10.31)</td>
<td>[ t_{73} = −5.76; P &lt; .001 ]</td>
</tr>
<tr>
<td>Adverse effects (sum score) b</td>
<td>48.88 (46.63 to 51.14)</td>
<td>49.30 (47.73 to 50.86)</td>
<td>[ t_{73} = −0.40; P = .68 ]</td>
</tr>
<tr>
<td>Temperature to induce VAS score 60 in °C b</td>
<td>44.64 (46.28 to 46.60)</td>
<td>46.53 (46.38 to 46.69)</td>
<td>[ t_{73} = 0.09; P = .40 ]</td>
</tr>
<tr>
<td>Treatment guess, % c</td>
<td>43.30</td>
<td>56.70</td>
<td>[ \chi^2_{1,73} = 7.33, P = .09 ]</td>
</tr>
<tr>
<td>Guessed oxytocin</td>
<td>53.50</td>
<td>46.50</td>
<td></td>
</tr>
<tr>
<td>Guessed placebo</td>
<td>43.30</td>
<td>56.70</td>
<td></td>
</tr>
</tbody>
</table>

Main effect of group: \[ t_{73} = 0.37; P = .75 \]
Main effect of condition: \[ F_{1,73} = 58.93; P < .001 \]
Interaction: \[ F_{1,73} = 4.93; P = .03 \]

We also present unpaired 2-sided t tests to directly compare the difference measure (ie, pain rating on control site minus pain rating on placebo site) between groups. Variables with only 1 measure per group (ie, sum score of adverse effects and temperatures required to induce an intensity of VAS score 60) are also compared between groups using 2-tailed 2-sample t tests.

To compare the frequency of correct treatment guesses between groups, a 2-sided \( \chi^2 \) test was conducted.

Within the context of the current study, oxytocin might have increased stress and anxiety response to the placebo manipulation. Further studies are needed to replicate our findings in larger clinical populations, identify the underlying mechanisms, and explore moderating variables such as sex or aspects of patient-physician communication.

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Author Contributions: Dr Bingel had full access to all of the data obtained in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Mr Kessner and Dr Sprenger contributed equally to this work. Study concept and design: Sprenger, Wiech, Bingel.
COMMENT & RESPONSE

Contaminated Methylprednisolone Injections

To the Editor Dr Malani and colleagues1 used a gadolinium-contrast magnetic resonance imaging (MRI) screening protocol in 172 patients who had received 1 or more spinal or paraspinal injections of highly contaminated methylprednisolone but had not presented for medical care. The authors reported abnormal MRI findings in 36 patients (21%); of these 36 patients, 35 met the definition for probable or confirmed fungal spinal or paraspinal infection.

I am concerned about the chronological sequence of MRI in relation to the last injection. The 218 study patients received at least 1 injection between August 9 and October 2, 2012, and the MRI protocol was launched on November 9, 2012, and continued until April 30, 2013. For the 35 cases of infection, the median lag time from last injection to abnormal MRI was long (87 days; range, 44-192 days). But no data were presented on the lag time for the 118 patients with normal MRI.

The authors also did not indicate whether there was a predetermined time to obtain MRI after the last injection. The median lag time to normal or equivocal MRI findings might have been much shorter than the long period reported for the cases with abnormal MRIs.

Although MRI is the modality of choice for imaging early spinal or paraspinal bacterial infections, it is not without shortcomings.2 In approximately 70% of cases, the typical features of bacterial spondylodiskitis are apparent on MRI within the first 4 weeks, whereas in a further 30% of cases, positive findings will be revealed only after 4 weeks.3 Moreover, in fungal spinal infections, much less is known about the time to MRI diagnosis, and it may be lower than in bacterial infections, as suggested by the findings of the authors.4 In addition, in proven cases of methylprednisolone-induced spinal fungal infection in Tennessee, MRI conducted at symptom onset identified abnormalities suggestive of infection in only 46%, with a median lag time from last injection of 18 days (upper range, 56 days).4 Whether MRI should be repeated in patients with a normal initial MRI is undetermined, but might be considered if there was a significantly shorter lag time from the last injection compared with patients with an abnormal initial MRI.

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