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Influence of Intranasal Epinephrine and Lidocaine Spray on Olfactory Function Tests in Healthy Human Subjects

Yong Gi Jung, MD1, Seung Yong Ha, MD1, Young-Gyu Eun, MD1, and Myung-Gu Kim, MD1

Abstract

Objective. Although topical decongestants and anesthetics are widely used in preparation for nasal endoscopy, no controlled trials have evaluated the effects of these agents on olfaction.

Study Design. Randomized double-blinded controlled trial.

Setting. Tertiary referral hospital.

Materials and Methods. The authors recruited 72 healthy subjects and randomly assigned them to 1 of 4 groups (control, phenylephrine group, lidocaine group, and both agents). After baseline tests with the Korean version of Sniffin’ Stick Test II (KVSS II), topical agents were applied to each nostril. Fifteen minutes later, repeat tests were carried out. Pre- and postspray results of the olfactory tests were compared, and the differences among groups were analyzed.

Results. The mean ± SD prespray KVSS II score of the study group was 30.2 ± 3.8, and there were no statistically significant differences among the study groups (P = .353). Mean ± SD pre- and postspray KVSS II scores were 29.0 ± 3.5 and 30.7 ± 3.7 (P = .128) in the control group, 30.6 ± 3.6 and 31.7 ± 3.3 (P = .262) in the phenylephrine group, and 31.4 ± 3.6 and 32.1 ± 3.1 (P = .557) in the lidocaine group, respectively. In the phenylephrine and epinephrine spray group, the mean ± SD pre- and postspray scores were 29.9 ± 4.4 and 31.3 ± 3.7 (P = .071), respectively.

Conclusions. Neither topical intranasal phenylephrine nor lidocaine use affected the results of the olfactory test, even when the agents were used in combination.

Keywords

smell, olfactory disorder, lidocaine, phenylephrine, toxicity tests, nasal decongestants, intranasal administration, topical administration

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For this reason, we sought to determine whether topical intranasal anesthetics (lidocaine) and decongestants (phenylephrine) influence olfactory function and if the combined use of these 2 agents has additional negative or positive effects.

**Materials and Methods**

**Study Design and Sample**

We designed a randomized, double-blinded, controlled trial and recruited healthy volunteers in their 20s and 30s with subjective nosomia and no nasal obstruction. This study was approved by the Institutional Ethics Committee of Samsung Changwon Hospital, and all subjects provided written consent prior to participation.

Subjects who had purulent rhinorrhea within 2 weeks before the olfactory test, purulent discharge, nasal polyp, or mucosal swelling on endoscopic examination of the nasal cavity; were taking an oral or topical vasoconstrictor or using steroids within 1 week before the tests; had experience with the olfactory test that was used in this study (to exclude the learning effect); and had a history of nasal surgery were excluded from this study.

**Study Protocols and Olfactory Tests**

All subjects were randomly assigned to 1 of 4 groups with 18 members each: (1) control, (2) epinephrine spray, (3) lidocaine spray, and (4) epinephrine and lidocaine spray. Sample size is addressed below.

Tests were conducted for 2 consecutive days. All subjects were asked not to drink alcohol on the evening before the olfactory test, to get enough sleep, and to refrain from smoking for at least 3 hours before the test.

On the first day, baseline olfactory tests (the Korean version of Sniffin’ Stick Test II [KVSS II]) were carried out without the application of any topical agents. On the second day, 2 sprays of 0.15 mL of normal saline (control) for group 1, 0.15 mL of 0.5% phenylephrine hydrochloride (Dong Kwan Pharm, Seoul, Korea) with saline for group 2, 0.15 mL of 4% lidocaine hydrochloride (Dai Han Pharm, Seoul, Korea) with saline for group 3, and 0.15 mL of 0.5% phenylephrine hydrochloride and 4% lidocaine hydrochloride for group 4 were delivered into each nasal cavity of the members of the respective groups with a powered air spray system. In groups 2 and 3, phenylephrine and lidocaine were applied after the normal saline to avoid a washing effect. Subjects were blinded to the types of nasal sprays as they were administered. One physician (S.Y.H.) delivered topical agents to all subjects to minimize variability. Subject positioning and direction of application are described in Figure 1. Fifteen minutes after spray application, olfactory tests were conducted in all subjects. Figure 2 is a diagram of the study protocol. The same well-trained examiner performed all olfactory tests blinded to subject treatment.

**Sample Size**

We planned a study of continuous response variables from matched pairs of study subjects. Through a pilot study using 5 subjects per group, we established that the standard deviation of the differences in variables was 3.8. The standard deviation of KVSS II results for nosomia is 5.3 based on a previous validation study, and we used this value to define effect size. We calculated that 18 subjects were required for each group to be able to reject the null hypothesis of no response difference with a probability (power) of 0.95. The type I error probability associated with tests of this null hypothesis was 0.05. We therefore set the power to 0.95 for the equivalence test.

**Korean Version of Sniffin’ Stick Test II**

The KVSS II is a modification of Sniffin’ stick test, and pens similar to Sniffin’ sticks are commercially available (Burghart Company, Weldel, Germany). Sniffin’ sticks are filled with the liquid odorant being tested. For odor presentation, the examiner removes the cap for 3 seconds and places the tip 2 cm in front of the subject’s nostrils. This test is composed of 3 different trials that create a total maximum score of 48: odor thresholds of 16 different concentrations of n-butanol, discrimination of 16 triplets of odorants, and identification of 16 items. The KVSS II has been accredited by the Korean Society of Otorhinolaryngology and was validated through comparisons with the Cross Cultural Smell Identification Test (CC-SIT).

**Clinical and Statistical Analysis**

The results of the KVSS II (total score and 3 individual parameters) between pre- and posttopical nasal applications of phenylephrine and lidocaine were compared using the paired $t$ test for each group. Analysis of variance (ANOVA) was employed to compare the ages of the study groups, and the $\chi^2$ test was used to compare gender ratios. $P$ values <
.05 were considered statistically significant. Statistical analyses were performed using SPSS software (version 12.0; SPSS, Inc, an IBM Company, Chicago, Illinois).

**Results**

**Characteristics of Enrolled Patients**

Seventy-two subjects satisfied the inclusion and exclusion criteria of this study between April 2010 and October 2010 and were enrolled in the study. There were 26 men and 46 women. No subjects were lost after enrollment and completion of the first olfactory test. The mean age of the enrolled subjects was 25.6 years. There were no statistically significant differences in age ($P = .277$) or gender ratio ($P = .564$) among study groups. The mean $\pm$ SD prespray KVSS II score of the study group was 30.2 $\pm$ 3.8, and there were no significant differences among the scores of study groups ($P = .353$). Demographic data and mean KVSS II scores for each group are shown in Table 1.

**KVSS II Scores**

The mean $\pm$ SD pre- and post-spray KVSS II scores were 29.0 $\pm$ 3.5 and 30.7 $\pm$ 3.7 ($P = 0.128$) in group 1 (normal saline twice), 30.7 $\pm$ 3.6 and 31.7 $\pm$ 3.3 ($P = .262$) in group 2 (phenylephrine and normal saline), 31.4 $\pm$ 3.6 and 32.1 $\pm$ 3.1 ($P = .557$) in group 3 (lidocaine and normal saline), and 29.9 $\pm$ 4.4 and 31.3 $\pm$ 3.7 ($P = .071$) in group 4 (lidocaine and phenylephrine), respectively. There were no significant differences between the pre- and postspray KVSS scores among the groups.

In addition, the differences in KVSS II score between pre- and postspray tests in each group were not significantly different ($P = .892$), and so there were no significant differences in postspray KVSS II score according to group ($P = .713$).

Comparing the KVSS II scores for each individual parameter, no specific agent, including phenylephrine, lidocaine, or the combination of both agents, demonstrated either positive or negative effects on butanol threshold, odor discrimination, or odor identification. Detailed data are shown in Tables 2 and 3.

**Discussion**

Neither topical phenylephrine nor lidocaine affected olfactory testing when applied intranasally, and there were also no differences between single-agent use and combined use. In addition, individual parameters of olfactory testing, such
as olfactory threshold, discrimination, and identification, were not affected by application of these topical sprays.

Our study is the first randomized controlled trial to address this issue. Our study design demonstrated high statistical power (0.95) for equivalence testing, yielding a strong level of confidence in our findings.

Total KVSS II scores slightly increased after application of the topical sprays, but the increases were not statistically significant, and slight increases were also observed in the control group. None of the subjects who were enrolled in this study had experience with olfactory tests prior to this study. We concluded, therefore, that the lack of significant increases in KVSS II scores for all of the groups was due to learning effects and that neither topical phenylephrine nor lidocaine had any effects on olfactory function.

We selected the KVSS II as a tool to measure olfactory function. The KVSS II is composed of 3 individual tests, including the butanol threshold test, the odor discrimination test, and the odor identification test. This test was designed after Sniffin’ stick test, although some of the items in the identification test (turpentine, cloves, cinnamon, and anise) were replaced with scents more familiar to Koreans (vanilla, resin, soy, and sesame oil), and it has been validated.3 The University of Pennsylvania Smell Identification Test (UPSIT), Cross-Cultural Smell Identification Test (CC-SIT), Connecticut Chemosensory Clinical Research Center (CCCRC), KVSS, and Toyota and Takagi (T&T) olfactometers are all available in Korea. Among the possible tests, we selected the KVSS test because it is the most detailed.

Until now, whether or not topical decongestants and anesthetics produce olfactory dysfunction has been unclear. Occasionally, anesthetics have been used by clinicians to purposely impede the ability to smell, particularly in the assessment and treatment of phantosmia.11 This possible side effect may be due to either direct toxic effects of the administered spray or decreased mucosal blood flow itself.12 In 1999, Temmel et al9 reported that ephedrine appeared to have neither negative nor major positive effects on intranasal chemosensory function. Reduced self-assessment of olfaction after intranasal anesthesia was reported in 2004.6 There have been no controlled studies investigating the combined use of topical anesthetics and decongestants, however, even for topical phenylephrine, one of the most widely used decongestants.

We enrolled only normal volunteers as study subjects, which was necessary to determine the effects of topical agents on olfaction without complications due to the clinical setting. With normal response levels established, we now plan to investigate the effects of topical decongestants and anesthetics on the olfactory function of subjects with either polyps or sinusitis in the near future.

### Table 2. KVSS Pre- and Postspray Scores in Individual Parameters of Each Study Group

<table>
<thead>
<tr>
<th>Group</th>
<th>KVSS Item</th>
<th>Pre</th>
<th>Post</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>T</td>
<td>6.1 ± 2.4</td>
<td>7.3 ± 2.1</td>
<td>.070</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>10.9 ± 2.0</td>
<td>11.0 ± 1.9</td>
<td>.900</td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>11.2 ± 2.5</td>
<td>12.3 ± 0.9</td>
<td>.105</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>29.0 ± 3.5</td>
<td>30.7 ± 3.7</td>
<td>.128</td>
</tr>
<tr>
<td>Phenylephrine spray</td>
<td>T</td>
<td>7.1 ± 2.8</td>
<td>8.4 ± 2.7</td>
<td>.120</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>11.1 ± 1.5</td>
<td>11.6 ± 1.6</td>
<td>.425</td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>12.5 ± 1.1</td>
<td>12.8 ± 1.1</td>
<td>.353</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>30.7 ± 3.6</td>
<td>31.7 ± 3.3</td>
<td>.262</td>
</tr>
<tr>
<td>Lidocaine spray</td>
<td>T</td>
<td>6.3 ± 1.8</td>
<td>6.7 ± 1.8</td>
<td>.479</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>12.4 ± 1.6</td>
<td>12.7 ± 2.0</td>
<td>.503</td>
</tr>
<tr>
<td></td>
<td>I</td>
<td>12.7 ± 1.2</td>
<td>12.7 ± 1.3</td>
<td>.860</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>31.4 ± 3.6</td>
<td>32.1 ± 3.1</td>
<td>.557</td>
</tr>
<tr>
<td>Both</td>
<td>T</td>
<td>6.1 ± 2.1</td>
<td>6.7 ± 2.6</td>
<td>.340</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>11.1 ± 1.9</td>
<td>11.2 ± 1.5</td>
<td>.550</td>
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<tr>
<td></td>
<td>I</td>
<td>12.7 ± 1.7</td>
<td>13.2 ± 1.5</td>
<td>.057</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>29.9 ± 4.4</td>
<td>31.3 ± 3.7</td>
<td>.071</td>
</tr>
</tbody>
</table>

Abbreviations: D, discrimination; I, identification; KVSS, Korean version of Sniffin’ Stick Test II; T, threshold.

### Table 3. Difference between Pre- and Postspray KVSS II Score in Each Study Group

<table>
<thead>
<tr>
<th>Group 1: Control</th>
<th>Group 2: Phenylephrine</th>
<th>Group 3: Lidocaine</th>
<th>Group 4: Both</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference</td>
<td>1.7 ± 4.0</td>
<td>1.1 ± 3.53</td>
<td>0.7 ± 4.2</td>
<td>1.4 ± 2.8</td>
</tr>
</tbody>
</table>

Abbreviation: KVSS, Korean version of Sniffin’ Stick Test II.
Conclusion

Topical intranasal phenylephrine and topical lidocaine, both alone and in combination, did not alter the outcomes of olfactory testing. Accordingly, we hypothesize that olfactory testing can be conducted either before or after the application of topical phenylephrine and/or lidocaine without affecting the accuracy of such tests.

Author Contributions

Yong Gi Jung, editing, data analysis; Seung Yong Ha, data collection; Young-Gyu Eun, revision; Myung-Gu Kim, revision.

Disclosures

Competing interests: None.
Sponsorships: None.
Funding source: None.

References