Cochrane for Clinicians
Putting Evidence into Practice

Saline Irrigation for Allergic Rhinitis
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Clinical Question: Is nasal saline irrigation an effective treatment for allergic rhinitis?

Evidence-Based Answer
Nasal saline irrigation reduces the severity of allergy symptoms for up to eight weeks vs. no treatment. It is uncertain if adding nasal saline to pharmacologic treatment further improves symptoms over pharmacologic treatment alone. It is also unclear whether there is any difference in symptom outcomes when comparing the use of nasal saline and intranasal corticosteroids. Nasal saline is well tolerated. (Strength of Recommendation: B, recommendation based on inconsistent or limited-quality patient-oriented evidence.)

Practice Pointers
Allergic rhinitis is an immunoglobulin E–mediated nasal hypersensitivity to allergens. It often presents as rhinorrhea, sneezing, and nasal itching and may include other symptoms such as conjunctivitis and ear pain or fullness. Patients with allergic rhinitis can also have impaired sleep and social interactions, leading to a decreased quality of life. The prevalence of allergic rhinitis in the United States currently varies between 10% and 30% for adults and up to 40% for children, making this a common condition encountered by the family physician.

This Cochrane review included 14 studies with a total of 747 participants (seven randomized controlled trials [RCTs], 260 adults; seven RCTs, 487 children) from China, Italy, Thailand, Turkey, and the United States. All of the studies were parallel-group RCTs; only two studies were described as single-blinded and the remaining 12 were nonblinded. The volume of saline used in the studies varied from less than 5 mL per nostril per application to more than 60 mL per nostril per application. The type of saline varied as well, ranging from hypertonic to isotonic. Treatment duration was one to 12 weeks across the different comparisons.

Primary outcomes included disease severity as measured by patient-reported symptom scores, including the Total Nasal Symptom Score (a five-item questionnaire with each question graded none, mild, moderate, or severe to evaluate nasal congestion, rhinorrhea, nasal itching, sneezing, and difficulty sleeping), visual analog scales, and other symptom scores. Because the results were reported using a variety of scores, data were calculated as mean difference and standard deviation. When different scales were used, the authors reported the standardized mean difference (SMD). The included studies were of low- to very low-GRADE quality. Adverse effects were not consistently reported in the studies. Only four studies specifically stated in their methods that adverse effects would be reported. Of the 10 studies that mentioned adverse effects, six reported only the effects in the nasal saline irrigation group; three studies reported adverse effects in both arms; and in the remaining study, it was not clear which allocated group experienced the adverse effects.

A meta-analysis of six studies (N = 407, 85 adults and 322 children) found that nasal saline irrigation may improve symptom scores compared with no saline or pharmacologic treatment at up to four weeks (SMD = –1.3; 95% CI, –1.8 to –0.8) and at eight weeks (five RCTs; N = 167, 65 adults and 102 children; SMD = –1.4; 95% CI, –2.4 to –0.5). When comparing nasal saline irrigation added to pharmacologic treatment (i.e., oral antihistamines or intranasal corticosteroids) vs. the same pharmacologic treatment alone, no additional differences were demonstrated. Similarly, no differences in primary outcomes were noted when nasal saline irrigation was compared with intranasal corticosteroid therapy. Epistaxis was not reported with saline in any of the included trials.

Guidelines state that an intranasal corticosteroid alone or an intranasal corticosteroid and an intranasal antihistamine are recommended as first-line treatment for seasonal and perennial allergic rhinitis. For seasonal allergic rhinitis, an oral antihistamine may be used in combination with an intranasal corticosteroid, and use of either an oral antihistamine or a leukotriene receptor antagonist is recommended. For perennial allergic rhinitis, oral antihistamines are preferred to leukotriene receptor antagonists. (Strength of...
Recommendation: C, based on consensus, disease-oriented evidence, usual practice, expert opinion, or case series.)

The practice recommendations in this activity are available at http://www.cochrane.org/CD012597.

References

Aromatase Inhibitors Such as Letrozole (Femara) vs. Clomiphene (Clomid) for Subfertile Women with PCOS
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Clinical Question
Compared with clomiphene (Clomid), are aromatase inhibitors such as letrozole (Femara) effective treatments for subfertile women with polycystic ovary syndrome (PCOS) who are trying to conceive?

Evidence-Based Answer
When treated with letrozole, subfertile women with PCOS who are trying to conceive have increased chances of pregnancy (number needed to treat [NNT] = 11) and live birth (NNT = 10) compared with those treated with clomiphene. The risk of adverse outcomes including miscarriage, ovarian hyperstimulation syndrome, and multiple pregnancy is not increased.1 (Strength of Recommendation: A, based on consistent, good-quality patient-oriented evidence.)

Practice Pointers
PCOS is the most common cause of oligomenorrhea and amenorrhea worldwide,1 affecting one in 10 U.S. women of childbearing age.2 Women with PCOS often experience anovulation. Clomiphene has been the most widely used treatment for infertility in this group. Both clomiphene and letrozole are given at the beginning of a menstrual cycle to improve the chances of ovulation and are followed by timed intercourse (or intrauterine insemination). The authors sought to determine if letrozole, an aromatase inhibitor, is as safe and effective as clomiphene for PCOS-associated infertility.

This Cochrane review included 42 randomized controlled trials (RCTs) comparing letrozole with clomiphene. The trials were from eight different countries and included a total of 7,935 women 18 to 40 years of age with anovulatory PCOS.3 Only one trial was performed in the United States. The primary analysis included studies of ovulation induction followed by timed intercourse. The quality of evidence was moderate for the primary outcome (live birth rate) and high for secondary outcomes (adverse effects).

In the analysis, women treated with letrozole vs. clomiphene had a higher incidence of live birth (treatment

SUMMARY TABLE: CLOMIPHENE (CLomid) VS. LETROZOLE (FEMARA) FOR SUBFERTILE WOMEN WITH POLYCYSTIC OVARY SYNDROME

<table>
<thead>
<tr>
<th>Outcomes with up to six months of treatment and timed intercourse</th>
<th>Probable outcome with clomiphene</th>
<th>Probable outcome with letrozole (95% CI)</th>
<th>NNT for outcome with letrozole (95% CI)</th>
<th>Number of participants (number of studies)</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy*</td>
<td>264 per 1,000</td>
<td>359 per 1,000 (330 to 390)</td>
<td>11 (8 to 15)</td>
<td>4,629 (25 RCTs)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Live birth rate</td>
<td>214 per 1,000</td>
<td>314 per 1,000 (279 to 352)</td>
<td>10 (7 to 15)</td>
<td>2,954 (13 RCTs)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Ovarian hyperstimulation syndrome</td>
<td>5 per 1,000</td>
<td>5 per 1,000 (5 to 6)</td>
<td>NA†</td>
<td>2,536 (12 RCTs)</td>
<td>High</td>
</tr>
<tr>
<td>Miscarriage rate</td>
<td>201 per 1,000</td>
<td>191 per 1,000 (150 to 240)</td>
<td>NA†</td>
<td>1,210 (18 RCTs)</td>
<td>High</td>
</tr>
<tr>
<td>Twin or other multiple pregnancy</td>
<td>17 per 1,000</td>
<td>13 per 1,000 (7 to 21)</td>
<td>NA†</td>
<td>3,579 (17 RCTs)</td>
<td>High</td>
</tr>
</tbody>
</table>

NA = not applicable; NNT = number needed to treat; RCT = randomized controlled trial.

*—Pregnancy was defined as the presence of a gestational sac on ultrasonography.
†—Results were not statistically significant.
difference = 10% [95% CI, 6.5% to 13.8%]; NNT = 10 [95% CI, 7 to 15]). Clinical pregnancy (defined as the presence of a gestational sac on ultrasonography) was more common with letrozole (treatment difference = 9.5% [95% CI, 6.6% to 12.6%]; NNT = 11 [95% CI, 8 to 15]). The absolute risk of ovarian hyperstimulation syndrome, resulting in ovarian enlargement, ascites, and occasionally more serious complications, was low (0.5%) and similar in both groups. Miscarriage rates (approximately 20% in each group) and multiple pregnancy rates (approximately 1.5% in each group) were also not significantly different.

Canadian and U.S. obstetric society guidelines were updated in 2018 to list letrozole as first-line medical therapy for women with anovulatory PCOS who are trying to conceive. Women should be counseled that use for this indication is still considered off-label in both countries. Letrozole and clomiphene are typically administered for five days starting on day 3, 4, or 5 of a patient’s menstrual cycle. Letrozole may be more cost-effective ($11.73 for 30 tablets compared with $30.47 for 30 tablets of clomiphene).

Editor’s Note: The numbers needed to treat, confidence intervals, and treatment difference percentages reported in this Cochrane for Clinicians were calculated by the author based on raw data provided in the original Cochrane review.

References