Is Noninhaled Intranasal Carbon Dioxide Gas a Safe and Effective Treatment for Improvement of Nasal Symptoms of Allergic Rhinitis?

Andrew R. Couchara
*Philadelphia College of Osteopathic Medicine, andrewcou@pcom.edu*

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Is Noninhaled Intranasal Carbon Dioxide Gas a Safe and Effective Treatment for Improvement of Nasal Symptoms of Allergic Rhinitis?

Andrew R. Couchara, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 14, 2012
ABSTRACT
OBJECTIVE
The objective of this selective EBM review is to determine whether or not noninhaled intranasal carbon dioxide (CO₂) gas is a safe and effective treatment for improvement of nasal symptoms of allergic rhinitis.

STUDY DESIGN

DATA SOURCES
Three randomized controlled trials published after 2007 were obtained using PubMed.

OUTCOMES MEASURED
Number of sneezes and severity of nasal symptoms (nasal congestion, rhinorrhea) were recorded by subjects using an ordinal scale to obtain a Total Nasal Symptom Score (TNSS). Scores recorded before and after treatment were compared to reflect effectiveness of treatment.

RESULTS
Casale TB, Romero FA, Spierings EL (2008) and Casale TB, Korenblat PE, Meltzer EO et al. (2011) demonstrated a high incidence of adverse events during gas administration – most commonly nasal stinging and watery eyes. Baroody FM, Gavanescu L, Wang JH et al. (2011) did not record incidence of adverse events during gas administration. Casale et al. (2008) reported a significant (>75%) improvement of nasal symptoms following treatment (26.7%) compared to placebo (3.4%). Baroody et al. (2011) reported significant improvement in sneezing and rhinorrhea only. Casale et al. (2011) established significant improvement in total nasal symptoms in only one experimental arm when the treatment was administered at 10mL/second x 10 seconds per nostril.

CONCLUSION
Evidence supporting the safety of noninhaled intranasal CO₂ gas therapy is inconclusive at this time due to lack of research addressing administration more frequent than single-use. Despite the high incidence of adverse events observed during single-use treatment, none of these effects were “serious” or “medically significant.” Evidence supporting the efficacy of this therapy is inconclusive at this time due to lack of reproducibility beyond the preliminary study with adequate blinding.

KEY WORDS
allergic rhinitis, noninhaled intranasal carbon dioxide, safety, nasal symptoms
INTRODUCTION

Allergic rhinitis (AR) affects approximately 20% of people in the United States\textsuperscript{1} as the 6\textsuperscript{th} most common ailment.\textsuperscript{2} Annually, patients with AR average three additional primary care visits, fill nine more prescriptions, and cost the healthcare system $1,500 more than patients without AR leading to an estimated 5.3 billion dollars in healthcare costs per year.\textsuperscript{3} AR symptoms may significantly affect an individual’s quality of life and may contribute to other comorbidities including asthma, rhinosinusitis, and otitis.\textsuperscript{2,4}

Current methods of symptom-directed therapy include the gold standard of allergen avoidance as well as nonpharmacotherapy (i.e. saline nasal lavage), and pharmacotherapy including antihistamines, corticosteroids, sympathomimetics, antileukotrienes, allergen immunotherapy, and immunomodulators.\textsuperscript{2,4,5} With the exception of topical sympathomimetics (i.e. oxymetazoline /Afrin\textsuperscript{®} nasal spray), no other current treatment for AR induces rapid relief from nasal symptoms.\textsuperscript{4} Even with topical sympathomimetics, use is limited to no more than three consecutive days due to the risk of developing subsequent rhinitis medicamentosa.\textsuperscript{4} Many individuals suffering from AR continue to have symptoms even after a combination of non-pharmacological and pharmacological treatment methods have been exhausted.\textsuperscript{4}

Preliminary evidence suggests that noninhaled intranasal carbon dioxide gas may provide rapid relief from symptoms of AR.\textsuperscript{2} Using this method, CO\textsubscript{2} gas is insufflated into one nostril at a time from compressed cylinders attached to tubing connected to a nosepiece. The user holds their breath or exercises mouth breathing while gas passes over the nasal mucosa, through the nose and sinus cavities, and out through the contralateral nostril.\textsuperscript{2,4}

The current trend of healthcare strongly suggests that primary care offices will soon be faced with unprecedented patient volumes – a progression that warrants greater focus on cost
saving measures including more effective treatment options for common ailments. If noninhaled intranasal CO₂ proves to be effective, clinicians will need to understand and offer it to patients as an additional treatment option. The combination of patient discomfort attributed to AR as well as increasing costs to the healthcare system deem research on this topic relevant to any physician, physician assistant, or nurse practitioner. This paper reviews three randomized controlled trials comparing noninhaled intranasal CO₂ gas therapy to placebo for safety and effectiveness of improvement of nasal symptoms of AR (nasal congestion, rhinorrhea, and sneezing).

OBJECTIVE

The objective of this selective EBM review is to determine whether or not noninhaled intranasal CO₂ gas is a safe and effective treatment for improvement of nasal symptoms of AR.

METHODS

The search for relevant articles started December 20, 2011 and ended February 7, 2012. Articles found using PubMed were selected based on relevance to the clinical question as well as their focus on patient-oriented evidence that matters (POEM). Keywords used to locate articles included, “allergic rhinitis,” “noninhaled intranasal carbon dioxide,” “safety,” and “nasal symptoms.” Article inclusion criteria were limited to randomized controlled trials written in English that were published in peer-reviewed journals. Exclusion criteria included studies that focused on participants under 18 years of age, studies that focused on disease-oriented evidence (DOE), and studies utilizing non-human models. After inclusion and exclusion criteria were met and considered, three studies fulfilled these requirements. They include: 1) Casale TB, Romero FA, Spierings EL (2008), a randomized, double-blind, placebo-controlled, parallel-group study; 2) Baroody FM, Gavanescu L, Wang JH et al. (2011), a randomized, two-way crossover study;
and 3) Casale TB, Korenblat PE, Meltzer EO et al. (2011), a randomized, double-blind, placebo-controlled, multicenter study.

Relevant articles were selected according to similarity of population, intervention, method of comparison, outcomes measured, and study type as a randomized controlled trial. The population was limited to otherwise healthy adults (18-75 years) with AR requiring pharmacotherapy. Participants in all studies were either treated with noninhaled CO₂ gas delivered intranasally or were given placebo (compressed room air or no gas at all). Only Casale et al. (2008) used a true placebo by administering compressed room air via the treatment apparatus. The comparison for the remaining two studies (Baroody et al. (2011) and Casale et al. (2011)) consisted of physically setting up the treatment apparatus to the subject’s nose without delivery of gas for a duration equivalent to each corresponding experimental arm’s duration of treatment. All studies measured improvement of nasal symptoms (rhinorrhea, nasal congestion, and sneezing) following treatment.

Casale et al. (2008) included POEM in the form of dichotomous data. The two other studies used here included POEM as continuous data. Statistics reported or used in these studies include p-values, relative risk reduction (RRR), absolute risk reduction (ARR), number needed to treat (NNT), absolute risk increase (ARI), number needed to harm (NNH), mean change from baseline, one-way analysis of variance (ANOVA), and analysis of covariance (ANCOVA).
Table 1. Demographics & Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th># pt</th>
<th>Age</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>W/D</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Casale et al. (2008)</td>
<td>RCT; Randomized double-blind, placebo-controlled, single-center, parallel group study</td>
<td>89</td>
<td>18-75</td>
<td>• Adults with ≥ 2 year history of seasonal AR requiring pharmacotherapy • (+) skin prick test to seasonal grass or mold allergens prevalent in Omaha, Nebraska, in May 2005</td>
<td>• Asthma (other than mild or intermittent) • Intranasal/inhaled/systemic CS use within 30 days • Use of potentially confounding meds • Clinically significant nasal d/o • Hx URI within 14 days • Rhinitis medicamentosa</td>
<td>0</td>
<td>Noninhaled intranasal CO₂ gas admin’d at: 10 mL/s x 60s per nostril from large-capacity compressed gas cylinders</td>
</tr>
<tr>
<td>Baroody et al. (2011)</td>
<td>RCT; Randomized two-way crossover study; not blinded</td>
<td>12</td>
<td>No data</td>
<td>• Healthy adults • ± mild asthma req. only prn bronchodilators • (+) skin prick test to grass/ragweed • (+) screening challenge w/ two-fold incr. in ipsi/contralateral nasal secretions s/p allergen challenge • Subjects outside their allergy season</td>
<td>• Asthma (other than mild or intermittent) • Use of any medications, antihistamines or LTRA ≥ 1 week, intranasal CS ≥ 1 mo. before enrollment and for the duration of the study</td>
<td>0</td>
<td>Noninhaled intranasal CO₂ gas admin’d at: 8.33 mL/s x 10s per nostril from large-capacity compressed gas cylinders</td>
</tr>
<tr>
<td>Casale et al. (2011)</td>
<td>RCT Randomized double-blind, placebo-controlled, multicenter, in-clinic study</td>
<td>348</td>
<td>18-65</td>
<td>• Adults with ≥ 2 yr history of perennial AR requiring pharmacotherapy • (+) skin prick test to perennial allergen within the prior 12 mos. • Pts with TNSS ≥6</td>
<td>• Asthma (other than mild or intermittent) • CS use within 30 days • Use of potentially confounding meds • Clinically significant nasal d/o • URI within 14 days • Serious comobidity • Pregnancy (current/plans/breast feeding) within 30 days</td>
<td>0</td>
<td>Noninhaled intranasal CO₂ gas admin’d at: 5mL/s x 10s 10mL/s x 10s 5mL/s x 30s 10mL/s x 30s per nostril from large-capacity compressed gas cylinders</td>
</tr>
</tbody>
</table>

TNSS = Total Nasal Symptom Score  
AR = allergic rhinitis  
CS = corticosteroid  
LTRA = leukotriene receptor antagonist  
URI = upper respiratory infection
OUTCOMES MEASURED

All three studies measured improvement of nasal symptoms (nasal congestion, rhinorrhea, and sneezing) following treatment using data derived from participant feedback. Casale et al. (2008) and Casale et al. (2011) measured nasal symptoms based on an ordinal scale from 0-5 (0, none; 1, little; 2, moderate; 3, quite a bit; 4, severe; 5, very severe). Baroody et al. (2011) measured nasal congestion and rhinorrhea based on an ordinal scale from 0-3 (0, none; 1, mild; 2, moderate; 3, severe) as well as total number of sneezes. In all three studies, Total Nasal Symptoms Scores (TNSS) were recorded by subjects before and after treatment to ultimately calculate mean change from baseline. Mean change from baseline between arms provided the means for comparison to determine the intervention’s effectiveness.

Both Casale et al. (2008) and Casale et al. (2011) subjected participants to an allergen nasal challenge, then provided time for them to mount an immune response (nasal symptoms) prior to administration of the treatment. In this case, mean changes from baseline derived from before and after treatment symptom scores reflected the treatment's ability to induce symptomatic relief. Alternatively, Baroody et al. (2011) subjected participants to the treatment first followed by the nasal allergen challenge. In this case, mean changes from baseline reflected the treatment's ability to prevent nasal symptoms.

Safety was determined by the incidence of adverse effects (if recorded) in each study. When possible, NNH was calculated using adverse event rate data and was considered along with the seriousness of these adverse events to help determine the safety of the intervention.

RESULTS

Efficacy

Casale et al. (2008) studied adults with a positive skin prick test response to seasonal grass or mold allergens prevalent in Omaha, Nebraska in May 2005. The authors reported 26.7%
of subjects who received CO₂ treatment achieved TNSS improvement greater than 75% from baseline at 30 minutes after treatment compared to only 3.4% of subjects who received placebo (p = .009). These values indicate a NNT equal to five to provide more than 75% relief of nasal symptoms.

Baroody et al. (2011) studied adults with a positive skin prick test response to either grass or ragweed allergens. The authors observed a clinically significant treatment effect (prevention) on sneezes as well as ipsilateral and contralateral nostril nasal symptoms after applying CO₂ at 8.33mL/s for 10 seconds per nostril.

Table 2. Baroody et al. (2011) Mean Change of Nasal Symptoms from Baseline TNSS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No-treatment Phase median (range)</th>
<th>CO₂-treatment Phase median (range)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sneezes (no.)</td>
<td>2.0 (0-14)</td>
<td>0 (0-5)</td>
<td>0.05</td>
</tr>
<tr>
<td>RN ipsi (score)</td>
<td>2.0 (0-6)</td>
<td>0.0 (0-4)</td>
<td>0.014</td>
</tr>
<tr>
<td>RN con (score)</td>
<td>2.0 (0-5)</td>
<td>0.0 (0-4)</td>
<td>0.014</td>
</tr>
<tr>
<td>SN ipsi (score)</td>
<td>2.0 (-1-6)</td>
<td>0.0 (-1-6)</td>
<td>0.1</td>
</tr>
<tr>
<td>SN con (score)</td>
<td>2.0 (-1-6)</td>
<td>0.0 (-1-6)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Ipsi = ipsilateral nostril to challenge; con = contralateral nostril to challenge; RN = runny nose; SN = stuffy nose.

Casale et al. (2011) studied adults with a positive skin prick test response to either dust mite, cockroach, cat, dog, or mold allergens. Study facilitators administered various dosages of CO₂ (at 5 and 10mL/s flow rates per nostril applied for 10 and 30 second durations) compared to placebo. When comparing mean changes from baseline, only one dosage (10mL/s/nostril x 10 seconds) provided a statistically significant treatment effect (p = .03). At 30 minutes after administration, susceptible subjects experienced peak symptom relief lasting at least four hours.

Table 3. Casale et al. (2011): Mean Change of TNSS from Baseline per Dosage

<table>
<thead>
<tr>
<th>Experimental Arm: CO₂ Dose</th>
<th>Mean change from baseline TNSS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: 5mL/s x 10s/nostril</td>
<td>-4.36</td>
<td>p = .09</td>
</tr>
<tr>
<td>B: 10mL/s x 10s/nostril</td>
<td>-4.69</td>
<td>p = .03</td>
</tr>
<tr>
<td>C: 5mL/s x 30s/nostril</td>
<td>-3.68</td>
<td>p = .86</td>
</tr>
<tr>
<td>D: 10mL/s x 30s/nostril</td>
<td>-4.58</td>
<td>p = .19</td>
</tr>
</tbody>
</table>

TNSS = Total Nasal Symptom Score
Safety

Casale et al. (2008) reported that no “serious” or “medically significant” adverse events occurred during this study. The most common adverse events that occurred included nasal stinging and watery eyes. 95% of experimental subjects experienced some degree of nasal stinging versus 44.8% of control subjects. 78.3% of experimental subjects experienced some degree of watery eyes compared to 27.6% of control subjects. The NNH for either nasal stinging or watery eyes was equal to one. Other adverse events reported by subjects included a nonspecific “swimmy feeling,” pharyngitis, headache, laryngitis, and stomach cramps. The authors contend that adverse events occurred only during gas administration and ceased before gas administration was terminated. Adverse events due to repeat treatments were not reported as only single-use treatment was studied.

Baroody et al. (2011) reported that subjects experienced a temporary burning sensation during CO2 administration. They reported that no other adverse effects resulted from the treatment. Before the allergen challenge was presented to subjects, sneeze counts as well as nasal and eye symptoms were recorded at baseline and then again after treatment. The change from baseline was recorded only after (but not during) gas administration. Using the comparison of symptoms from before and after treatment, the authors reported that CO2 administration caused no significant adverse events (p > 0.05). Adverse events due to repeat treatments were not reported as only single-use treatment was studied.

Casale et al. (2011) reported the most common adverse events included nasal discomfort, headache and lacrimation – all of which resolved upon cessation of gas administration without intervention. Other adverse events reported include rhinalgia, rhinorrhea, throat irritation, increased blood pressure, and dizziness. The single most common adverse event reported in
Group B was nasal discomfort which was reported by 81.4% of subjects in the experimental group versus only 8.3% in the control group. Nasal discomfort induced by the intervention demonstrates a NNH equal to one. Adverse events due to repeat treatments were not reported as only single-use treatment was studied.

Table 4. Casale et al. (2011): Most common adverse events in Group B (10mL/s/nostril x 10s)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>EER % (Group B)</th>
<th>CER % (Placebo)</th>
<th>NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal discomfort</td>
<td>81.4</td>
<td>8.3</td>
<td>1</td>
</tr>
<tr>
<td>Lacrimation incr.</td>
<td>27.1</td>
<td>2.8</td>
<td>4</td>
</tr>
<tr>
<td>Headache</td>
<td>8.6</td>
<td>13.9</td>
<td>-18</td>
</tr>
<tr>
<td>Rhinalgia</td>
<td>8.6</td>
<td>2.8</td>
<td>17</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>2.9</td>
<td>2.8</td>
<td>1000</td>
</tr>
<tr>
<td>Throat irritation</td>
<td>8.6</td>
<td>0.0</td>
<td>11</td>
</tr>
<tr>
<td>Blood pressure incr.</td>
<td>1.4</td>
<td>5.6</td>
<td>-23</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2.9</td>
<td>0.0</td>
<td>34</td>
</tr>
</tbody>
</table>

EER = experimental adverse event rate, CER = control adverse event rate, NNH = number needed to harm

None of these studies reported any withdraw of subjects from participation due to intolerability to treatment adverse effects.

**DISCUSSION**

Demonstrating statistically significant effectiveness (p-value = .009) and a low NNT (five), Casale et al. (2008) was the only study examined in this review that was devoid of potentially confounding factors. Maintenance of blinding measures or lack thereof proved to be the greatest limitation to the validity of Baroody et al. (2011) and Casale et al. (2011) as true RCTs. While Casale et al. (2008) administered compressed room air to the control group, Baroody et al. (2011) and Casale et al. (2011) applied the physical apparatus without administering gas of any type. Baroody et al. (2011) reported that neither researchers nor subjects were blinded to the knowledge of the phase of the two-way crossover in which they were participating. Casale et al. (2011) reported being unclear whether blinding was preserved or lost. Additionally, Casale et al. did not maintain intention-to-treat analysis. If subjects did not
complete one or more symptom assessments, they were omitted from the analysis for that time point. This may have exaggerated the strength of the treatment effect. Statistically significant efficacy demonstrated by both Baroody et al. (2011) and Casale et al. (2011) must be viewed with consideration given to these potentially confounding elements.

For the duration of these three studies, no subjects experienced any serious adverse events. Similarly, none of the authors reported any fallout due to therapy intolerability. Though the severity of adverse events following single-dose treatment may not have been great, NNH with regards to nasal stinging was equal to one. NNH with regards to watery eyes ranged from one to four depending on the dose delivered. These low numbers needed to harm indicate a high incidence of discomfort induced by a single dose of therapy. Unfortunately, the high recurrence of symptoms experienced by many individuals who suffer from AR (especially seasonal AR) makes chronic use of such a rapid therapy more likely than one-time use. Chronic use would further subjects users to these adverse effects and has not yet been studied.

Carbon dioxide gas was administered in these studies by appropriate tubing attached to large-capacity compressed gas cylinders. While this apparatus is not practical, Casale et al. (2008) cited a less cumbersome hand-held version currently being used for migraine treatment research that will be used in future studies. At this time, noninhaled intranasal CO₂ therapy is not commercially available as its use remains investigational. 

Treatment cost was not discussed in these articles.

CONCLUSION

At this time, the evidence is inconclusive to suggest that noninhaled intranasal carbon dioxide gas is a safe and effective treatment for nasal symptoms of AR. Of these three studies, only Casale et al. (2008) maintained adequate blinding. The lack of blinds in Baroody et al.
(2011) and Casale et al. (2008) may have confounded their data and consequently compromised the validity of their results. Despite a promising treatment effect observed by Casale et al. (2008) supported by high quality research methods, these results must be reproduced before effectiveness can be concluded.

Regarding safety of therapy, extremely low NNH for the most common adverse events (nasal stinging and watery eyes) indicate a very high incidence of these events experienced by subjects. The fact that these adverse effects almost always ceased upon cessation of gas flow indicates low danger following single-use treatment. However, despite this seemingly safe short-term adverse event profile, chronic use must be studied to identify any new adverse events or worsening of nonserious adverse events over time (i.e. mucosal desiccation) before safety can be properly evaluated. Recognition of adverse effects from repeated use would be necessary to more accurately assess the safety of this treatment.

To assess the safety and efficacy of noninhaled intranasal CO₂ gas compared to current available therapies that induce rapid symptomatic relief (i.e. oxymetazoline), these two therapies should be compared side-by-side in the same study. Future studies should attempt to establish the safety of chronic use, the side effects of potential abuse (as is often seen with Afrin®), comparison with existing therapies including intranasal and oral antihistamines, and reproducibility of results with a standard dosage.
References


