Original Article

Nasal Carbon Dioxide Used As Needed in the Symptomatic Treatment of Seasonal Allergic Rhinitis

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What is already known about this topic? Nasal, noninhaled carbon dioxide (CO_2) has been shown to be effective for the treatment of symptoms of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis in single application studies.

What does this article add to our knowledge? On the basis of the results of this study, it appears that the nasal, noninhaled CO_2 device is effective for the as-needed treatment of all principal SAR symptoms with a rapid and large effect size.

How does this study impact current management guidelines? The nasal, noninhaled CO_2 device represents a novel option for a safe and rapidly effective addition to the medical armamentarium for as-needed relief of SAR symptoms.

BACKGROUND: Nasal, noninhaled carbon dioxide (CO_2) was shown to be effective for the treatment of symptoms of seasonal allergic rhinitis (SAR) and perennial allergic rhinitis in single application studies.

OBJECTIVE: To assess the efficacy of as-needed treatment with nasal, noninhaled CO_2 in patients with SAR.

METHODS: Fifty-six ragweed-allergic patients were enrolled at 3 sites in this study. After a 3- to 7-day run-in, 32 eligible patients who had an instantaneous total nasal symptom score of 8 or more out of a maximum of 12 in at least 2 SAR episodes per day were randomized to the CO_2 group (n = 19) or to the placebo group (n = 13). A 10-second/nostril application was used as needed for 14 days (maximum 6 times/d). Patients evaluated their symptoms before and 30 minutes after each application. All symptoms were scored on a 0 to 3 scale.

RESULTS: Analysis of all treated episodes (CO_2 = 816, placebo = 516) showed a statistically significant beneficial change in total nasal symptom score from baseline (effect size = −0.51; $P < .001$). The effect size was larger with more severe baseline symptoms (baseline severities of ≥6 = −0.98; ≥8 = −1.14; and ≥10 = −1.61; all $P < .001$). CO_2 was well tolerated, with transient nasal discomfort as the most common adverse event reported. There were no serious adverse events, serious adverse device effects, or early discontinuations.

CONCLUSIONS: Nasal, noninhaled CO_2 is effective for the as-needed treatment of SAR symptoms. The effect is rapid and the effect size is large. It represents a novel potential option for the as-needed treatment of rhinitis symptoms. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: *Carbon dioxide; Nasal; Noninhaled carbon dioxide; CO_2; Seasonal allergic rhinitis; Treatment*

Allergic rhinitis (AR) affects between 10% and 30% of the population.[1] The prevalence of AR continues to increase worldwide.[1] The disease is associated with significant morbidity, reduced productivity, lost school days, and cost. In the United States alone, the total direct and indirect annual costs associated with AR are more than $11 billion.[2]

Rhinitis is characterized by the presence of 1 or more of the nasal symptoms of congestion, rhinorrhea, sneezing, and itching. Nonnasal symptoms such as itchy ear and throat, lacrimation, itchy eyes, and eye redness are often present as well. Other associated symptoms include headache, postnasal drip, fatigue, cognitive impairment, and sleep disturbance. Comorbid conditions such as asthma, sinusitis, and sleep apnea often exist as well.[3,4]

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Abbreviations used
AR- Allergic rhinitis
AE- Adverse event
CO_2- Carbon dioxide
SAR- Seasonal allergic rhinitis
TNNSS- Total nonnasal symptom score
TNSS- Total nasal symptom score

AR fundamentally involves nasal mucosal inflammation as a result of exposure to allergens. Seasonal AR (SAR) results from exposure to seasonal allergens (such as ragweed, cedar, and grass), whereas perennial AR results from exposure to allergens such as dust mites, occupational allergens, and molds. The early-phase symptoms are typically sneezing, itching, and rhinorrhea, whereas congestion is predominantly a late-phase symptom.[3]

An investigational product to deliver nasal, noninhaled carbon dioxide (CO_2) has been studied for the treatment of AR. Rapid relief from symptoms has been seen after single doses in symptomatic patients with SAR[5,6] and perennial AR.[7] The primary mode of action appears to be mechanical in nature. A brief 10-second wash per nostril cleanses the nasal passage and displaces allergens much like other washes. A longer duration of exposures may lead to chemical changes but does not appear to be the mechanism for such rapid relief of symptoms.[8,9] In this study, we assessed whether the nasal CO_2 device used only as needed would provide relief to patients for symptoms of SAR over a 2-week period.

METHODS

This was a randomized, double-blind, placebo-controlled, multicenter, parallel group, pilot study (ClinicalTrials.gov identifier: NCT 00917020) conducted in the United States at 3 clinical research centers: Atlanta Allergy and Asthma Research Department (Woodstock, Ga), the Clinical Research Center (St Louis, Mo), and Midwest Clinical Research, LLC (St Louis, Mo). The Sterling Institutional Review Board (Atlanta, Ga) reviewed/approved this study and protected the rights and welfare of the participants throughout the study. All patients signed an approved informed consent form before any study procedures. This study evaluated the efficacy and safety of a nasal, noninhaled CO_2 application (nasal CO_2 device) used as needed, up to 6 times a day, in patients with SAR. Approximately 50 patients who met the eligibility criteria were to be enrolled into this study to ensure that approximately 30 patients completed the study.

During a 3- to 7-day run-in period, patients rated their SAR symptoms in a paper diary during at least 2 SAR episodes per day (the interval in between episodes must be at least 2 hours). Patients were instructed to assess episodes that they believed had symptoms that were severe enough to warrant treatment. In addition, patients rated their SAR symptoms in the morning (eg, when they woke up) and in the evening (eg, before they went to sleep). These morning and evening diaries were reflective and were to indicate how patients felt over approximately the last 12 hours.

After the run-in period, patients returned to the clinical research center for a review of their diary data and to assess eligibility for randomization. Once eligibility was confirmed, patients were randomized to 1 of 2 treatment groups in an approximate 2:1 (active:placebo) ratio in blocks of 6. A 2:1 randomization was selected to provide the opportunity for more patients to be assigned and exposed to the CO_2, the active arm. The randomization list was generated using an SAS program (SAS Institute, Cary, NC) by a statistician independent from the study. Only the independent statistician and the clinical supply organization had access to the randomization list during the conduct of the study. Unblinding occurred after the completion of study assessments for all patients and after the database had been locked. The clinical supply organization generated a treatment kit assignment log for each site, which consisted of a list of treatment kits based on the order of treatment arm assignment (CO_2 or placebo). Once the site confirmed that a patient was eligible, they would assign the treatment kits to eligible patients in sequential order. Two treatment kits were dispensed to each patient so that the first set of 2 treatment kits (eg, 1a and 1b) was dispensed to the first patient randomized at the site, the second set of 2 treatment kits (eg, 2a and 2b) was dispensed to the second patient randomized at the site, and so on. The treatment kits consisted of a handheld device containing CO_2. The active nasal CO_2 device was calibrated to deliver CO_2 at 0.5 standard liters per minute. The placebo for the nasal CO_2 device was identical in appearance to the active device but was designed not to dispense the CO_2 to the nasal cavity.

TABLE I. Symptom scores

Symptom score	Symptoms used to determine symptom score*	Minimum score	Maximum score
TNSS	Average of left nostril nasal congestion and right nostril nasal congestion, runny nose, itchy nose, and sneezing	0	12
TNNSS	Lacrimation, eye redness, ear/throat itching, and eye itching	0	12

*Each symptom was rated on the basis of a 0-3 scale: none (0) = no sign/symptom evident; mild (1) = sign/symptom clearly present, but minimal awareness; easily tolerated; moderate (2) = definite awareness of sign/symptom that is bothersome but tolerable; severe (3) = sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping.

Patients used the nasal CO_2 device or placebo for 10 seconds/nostril, once on day 0 in the clinic. They then used the nasal CO_2 device or placebo for 10 seconds/nostril, as needed up to 6 times a day (the interval in between uses was required to be at least 2 hours), on days 1 to 14 inclusive. They documented their use (ie, date, time, and duration of application to each nostril) in the patient diary.

On day 0, randomized patients completed instantaneous symptom assessments immediately before (ie, no more than 10 minutes before) the use of the nasal CO_2 device or placebo; at 10, 30, and 60 minutes; and 4 and 6 hours after use of the nasal CO_2 device or placebo. On days 1 to 14, patients assessed their symptoms in a paper diary immediately before each use and approximately 30 minutes after each use. In addition, patients rated their SAR symptoms in the morning (eg, when they woke up) and in the evening (eg, before they went to sleep).

All SAR episode-related assessments, preuse assessments, and 30-minute postuse assessments were instantaneous assessments (ie, the symptom severity rating at the time of the assessment). The morning and evening assessments were reflective assessments (ie, the symptom severity rating since the previous reflective assessment; assessments were ~ 12 hours apart).

Patients self-rated the severity of their nasal (runny nose, congestion, sneezing, and itching) and nonnasal (lacrimation, eye redness, ear/throat itching, and eye itching) symptoms as well as postnasal drip and headache. Total nasal symptom scores (TNSS) and total nonnasal symptom scores (TNNSS) were calculated on the basis of the ratings and are presented in Table I.

Diagnosis and main criteria for eligibility

Males or females aged 18 to 65 years were eligible for the study if they were able to comply with the requirements of the protocol and gave written informed consent. Patients had a minimal 2-year history of SAR requiring pharmacotherapy and a positive skin test result to 1 or more seasonal allergens prevalent in the respective local geographical area during the study period.

Patients could not have a history of asthma (other than mild intermittent), nasal disorders (eg, deviated septum, nasal polyposis, rhinitis medicamentosa, or chronic rhinosinusitis) that were clinically significant, acute or significant sinusitis or upper respiratory tract infection within 14 days of enrollment, or an existing serious medical condition (eg, severe emphysema) that precludes participation. Patients who had participated in a previous study with nasal CO_2 were not eligible.

Before enrollment, patients were required to continue to meet all inclusion criteria, and avoid meeting any of the exclusion criteria. Protocol-specified washout of all nasal or systemic decongestants, antihistamines, or nasal steroids was to be completed before enrollment. Before randomization, patients had to continue to meet all eligibility criteria, not take any medications requiring washout, complete and have a minimum TNSS of 8 or more out of a maximum of 12 in at least 2 SAR episodes captured in their diaries in the 3 days before planned randomization, and complete at least 6 of the 7 morning and evening reflective diaries in the 3 days before randomization and in the morning of day 0.

Statistical methods

The sample size was based on each patient treated with study treatment on average 2 times a day. If 30 patients were treated 2 times a day for 14 days, there would be 840 treatment assessments, with 280 in the placebo arm and 560 in the CO_2 arm. This number of assessments was sufficient to have more than 80% power to detect a difference of 0.5 in TNSS change from baseline, defined as the difference between the immediate preuse and 30-minute postuse assessments in the CO_2 group versus the placebo group with a 2-sided α of 0.05. The calculation assumed a common SD of 2.0 and a placebo change from baseline of −1.8.

The primary efficacy end point was the response to treatment over the 14-day treatment period as assessed by change in TNSS. The change in TNSS at the 30-minute postuse assessment compared with the preuse assessment immediately preceding that application was compared between the active and placebo groups. In this analysis, the P value for the change in baseline was from an analysis of covariance (using an SAS program) with baseline score (preuse TNSS) as a covariate. To assess whether the treatment effect was present in a "per-patient" analysis (rather than a "per-episode" analysis), we evaluated the change from preuse TNSS in patients who received placebo (n = 13) versus active treatment (n = 19). Several other efficacy variables were also prospectively identified for exploratory analyses: change in individual symptoms, TNNSS, and over the 14-day period of use. Time to onset of effect, time to maximal effect, and duration effect were also examined. Because of the exploratory nature of these analyses, no adjustments for multiplicity were planned. The primary safety end point was the occurrence of adverse events (AEs). Additional safety assessments included physical examination findings, vital signs, nasal mucosal examination, and urine pregnancy tests.

RESULTS

Fifty-six ragweed-allergic patients were enrolled and a total of 32 patients were randomized and treated in this study (19 in the CO_2 group and 13 in the placebo group) at 3 sites in the United States from August 17, 2009 (first patient screened), to October 21, 2009 (last patient observation). No significant protocol violations were identified, and all patients were included in the intent-to-treat analysis (Figure 1). Table II presents the demographic and clinical characteristics of patients enrolled in the intent-to-treat group.

The primary efficacy analysis centered on the change in symptom scores (ie, 30-minute postuse TNSS compared with the preuse TNSS; Table III). Overall, there were 516 assessments included in the analysis from the placebo group and 816 assessments included from the CO_2 group. The mean change from preuse in the placebo group was -1.49 ± 1.86 and in the CO_2 group it was -2.00 ± 2.19. The difference between treatment groups (effect size, −0.51) was statistically significant ($P < .001$; Figure 2).

In addition, the change from preuse TNSS to 30-minute postuse TNSS in patients who received placebo (n = 13) versus active treatment (n = 19) was evaluated. The absolute difference in TNSS was 0.71 between the 2 groups ($P = .1$, analysis of covariance). Although the difference does not reach statistical significance, the absolute change from baseline is similar to that seen in the per-episode analysis, suggesting that the treatment effect is more likely to exist.

An exploratory analysis of the change in TNSS at the 30-minute postuse assessment from the preuse assessment was performed with the subset of assessments in which the preuse TNSS was 6 or higher, 8 or higher, or 10 or higher. The difference between treatment groups in all treated episodes and each subgroup was statistically significant ($P < .001$; Figure 2). Although the differences between baseline values and 30-minute postuse assessments were fairly consistent in the placebo arm, the active treatment group had a greater degree of improvement with higher baseline symptom scores. The change in TNSS from preuse was significantly greater in the CO_2 group compared with the placebo group during both weeks of the study (Table IV).

Time to onset of effect (defined as the point at which the active group first showed a statistically significant difference from the placebo group on the basis of a direct pairwise comparison at each time point) was day 1 beginning after the first dose. This significant difference between the active and placebo arms was also apparent on 7 of the 14 days, including the last day of treatment—day 14 (Figure 3).

For all nasal symptoms (ie, nasal congestion, runny nose, itchy nose, and sneezing), the mean preuse score was significantly higher in the placebo group, but the CO_2 group had a significantly greater decrease from baseline at 30 minutes postuse, indicating that nasal CO_2 was effective on all nasal symptoms (Figure 4). The differences between baseline scores and 30-minute postuse assessments in the active treatment group were greater for each nasal symptom when the baseline scores were 8 or higher.

The change in instantaneous TNNSS at the 30-minute postuse assessment from the preuse assessment immediately preceding that dose was compared between the 2 groups. Overall there were 514 assessments included in the analysis from the placebo group and 812 assessments included from the CO_2 group. The mean change from preuse for the placebo group was -0.87 ± 1.51 and in the CO_2 group it was -0.94 ± 1.48. This resulted in a statistically significant difference between

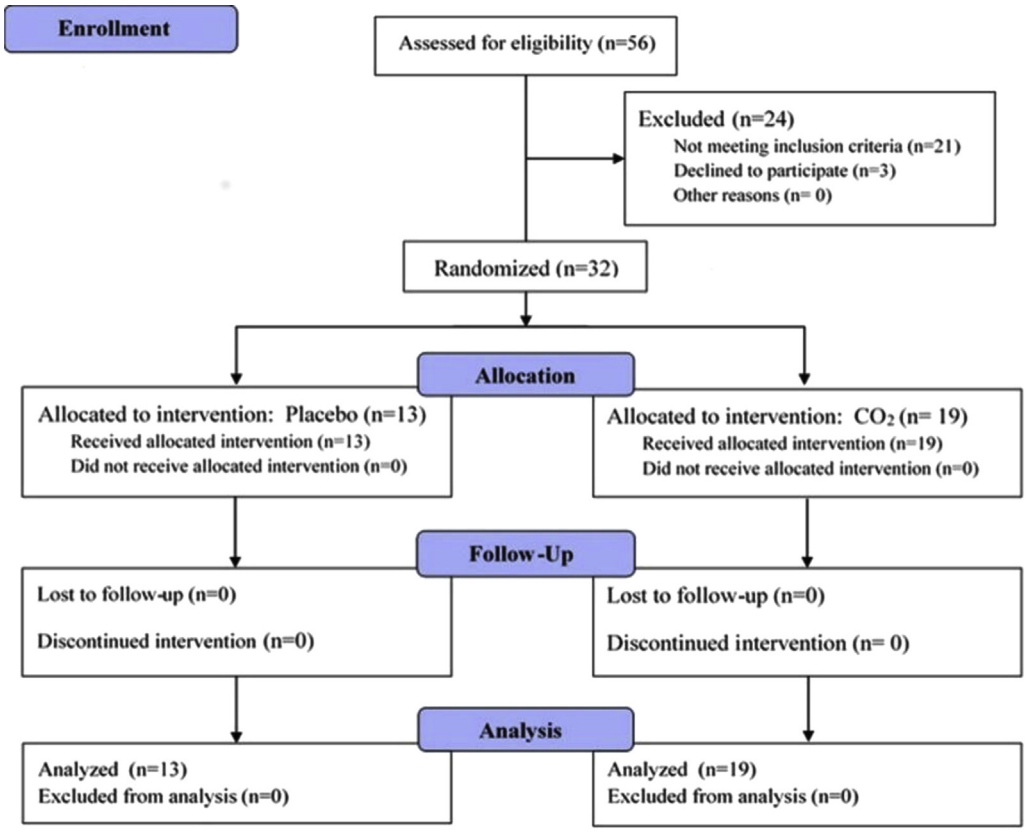

FIGURE 1. Study flow diagram.

TABLE II. Characteristics of the intent to treat population by treatment group

Characteristic	Placebo (n = 13)	CO_2 device (n = 19)
Age (y)		
Mean ± SD	33.1 ± 9.1	39.3 ± 8.8
Range	20-47	28-59
Sex		
Male	38.5%	31.6%
Female	61.5%	68.4%
Ethnicity, not Hispanic or Latino	100.0%	100.0%
Race		
Black or African American	38.5%	21.1%
White	61.5%	78.9%
Seasonal allergens*		
Ragweed	100%	100%
Grass	76.9%	78.9%
Tree	76.9%	68.4%
Other	53.8%	94.7%

*Most patients were polysensitized.

treatment groups but a small effect size of −0.08 ($P = .0015$). Nasal CO_2 is a local treatment and is not expected to have an effect on nonnasal symptoms.

The baseline reflective mean TNSS was similar between the 2 groups (placebo mean of 9.98; CO_2 mean of 9.66). The mean change from baseline in reflective TNSS in the placebo group was −1.97 ± 2.16 and in the CO_2 group it was −2.69 ± 2.28. This resulted in a large difference between treatment groups (effect size, −0.72) ($P = .43$).

Extent of exposure and safety results

All patients completed the planned treatment period. This device was simple to use and there were no patient-reported problems with using the device. The mean number of doses per patient was 41.3 ± 15.0 in the placebo group, ranging from 16 to 61, and 43.9 ± 19.6 in the CO_2 group, ranging from 5 to 71. Patients administered nasal CO_2 or placebo as needed but the interval between uses had to be at least 2 hours with no more than 6 doses per day. The average number of doses per patient per day was similar between both groups, 2.8 ± 0.9 in the placebo group and 3.0 ± 1.1 in the CO_2 group, which would be expected when patients were told to dose in this manner. The number of doses administered was similar on all study days. Overall, 78.1% of patients administered 2 or more doses per day on average, 46.9% administered 3 or more doses per day, and 31.3% administered 4 or more doses per day. No patient had an average of 5 or more doses per day.

Overall, 38.0% of study treatments were administered between 6 AM and noon, 32.1% between noon and 6 PM, and 26.3% between 6 PM and midnight.

Overall, 50.0% of patients had AEs during the study, including 23.1% in the placebo group and 68.4% in the CO_2 group. AEs were generally mild or moderate in severity and study

TABLE III. Change in instantaneous TNSS—all assessments, intent to treat patients

TNSS	Placebo (n = 13)	CO_2 (n = 19)	Difference	*P* value*
Preuse TNSS				
N	526	819		
Mean ± SD	8.54 ± 2.64	7.05 ± 3.19	−1.49	<.001
Median	9.00	7.00		
Minimum-maximum	0.50 to 12.00	0.00 to 12.00		
30-min postuse TNSS				
N	516	816		
Mean ± SD	7.03 ± 3.03	5.05 ± 3.19	−1.99	<.001
Median	7.00	5.00		
Minimum-maximum	0.00 to 12.00	0.00 to 12.00		
Change from preuse TNSS				
N	516	816		
Mean ± SD	−1.49 ± 1.86	−2.00 ± 2.19	−0.51	<.001
Median	−1.00	−1.50		
Minimum-maximum	−8.00 to 3.00	−11.00 to 3.00		

**P* values for preuse and 30-min postuse TNSS are from *t* tests. *P* value for the change from baseline is from an analysis of covariance with baseline score (preuse TNSS) as a covariate.

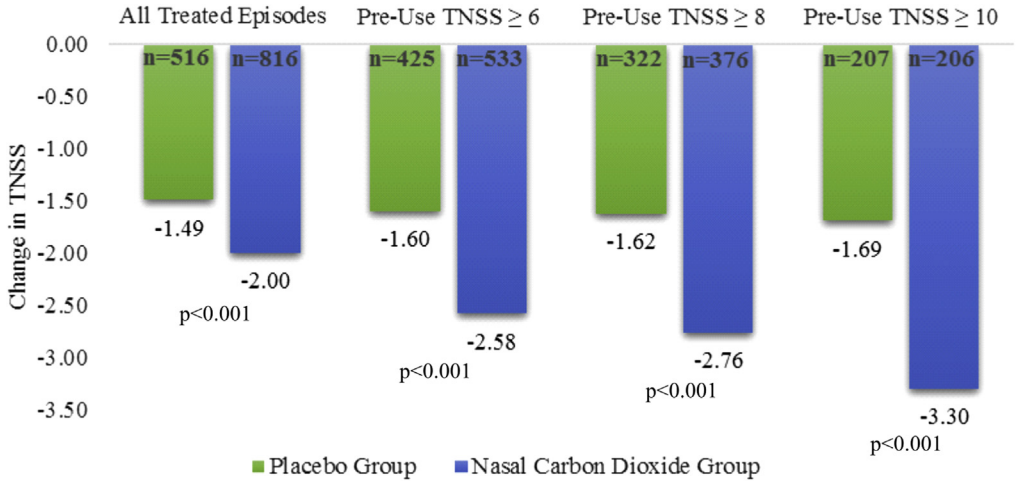

FIGURE 2. Change from preuse TNSS at 30 min. *P* value for the change from baseline is from an analysis of covariance with baseline score (preuse TNSS) as a covariate.

TABLE IV. Change from preuse instantaneous TNSS by week—all assessments, intent to treat patients

	Placebo (n = 13)		CO_2 (n = 19)			
Week	No. of assessments	Change, mean ± SD	No. of assessments	Change, mean ± SD	Difference	*P* value*
1	260	−1.61 ± 1.87	400	−1.93 ± 2.14	−0.31	<.001
2	256	−1.36 ± 1.85	416	−2.07 ± 2.12	−0.71	<.001

**P* values are from analysis of covariance with baseline score (preuse TNSS) as a covariate.

treatment—related and were resolved immediately upon cessation of the 10-second application. The most common AEs were transient nasal discomfort (15.4% placebo, 57.9% CO_2), lacrimation increase (7.7% placebo, 10.5% CO_2), headache (0.0% placebo, 10.5% CO_2), and dizziness (0.0% placebo, 10.5% CO_2). Most of these common AEs were considered related to study treatment. Only 3 patients on active treatment had severe AEs (nasal discomfort, dizziness, and somnolence). There were no serious AEs, serious adverse device effects, or withdrawals due to AEs in this study.

Vital signs (systolic and diastolic blood pressure, temperature, pulse, and respiration) were compared between treatment groups

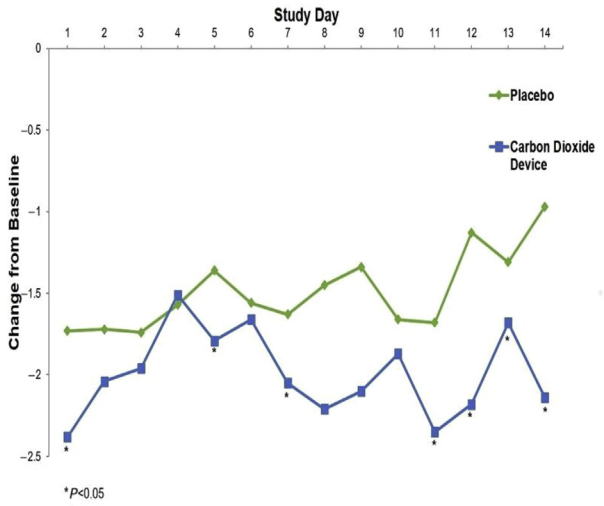

FIGURE 3. Difference between active and placebo TNSS (days 1-14).

on day 0 (first application of study treatment) at 30-minute preuse and 30-minute postuse assessments. No clinically significant effect of the placebo or active treatment was apparent.

Nasal mucosal examinations were performed at randomization and end-of-treatment visits. There were no clinically significant findings on nasal mucosal examination at randomization or the end-of-treatment visit.

DISCUSSION

The nasal CO_2 device has been shown to have a rapid effect across all symptoms of AR in earlier studies, as soon as 10 minutes in some patients.[6] The effect was replicated in the present study, which was designed specifically to assess the "as-needed only" treatment option for patients with SAR in ragweed season. It is important to recognize that this study was not designed as a well-powered efficacy study to conclusively answer the question of whether CO_2 works. It was, in fact, designed as a phase II study to test a hypothesis about the clinical utility of using intranasal CO_2 in an as-needed manner.

Significant baseline imbalances (in favor of a placebo response) were seen in the TNSS. The mean instantaneous TNSS (as well as all individual nasal symptoms) was significantly greater at preuse in the placebo group (8.54) than in the CO_2 group (7.05) ($P < .001$). Despite this difference, which favors the placebo group, the change from preuse to 30-minute postuse was significantly greater in the CO_2 group (effect size, -0.51; $P < .001$). It is very difficult to compare the effect size noted in this trial with the effect sizes for other approved therapies for AR. This study design is unique in that we investigated an as-needed therapy 30 minutes after the onset of use over a 2-week period. Nonetheless, intranasal CO_2 significantly improved all principal symptoms of AR, which is not typically demonstrated by other approved AR therapies even when given chronically. In addition, the percentage improvement as evident by the figures is large and very likely to be clinically meaningful. Head-to-head trials with other therapies using a similar design would be necessary to discern similarities and differences between intranasal CO_2 and other AR therapies.

Patients, who were asked to use the device "as needed" up to 6 times a day, used it on average about 3 times. That correlates well with an expected 4 to 6 hours effect of a single dose during waking hours. The effect was seen across all uses and on most study days, with the largest effect being seen on day 14. Therefore, no tachyphylaxis was observed.

Both the active nasal CO_2 device and placebo device were well tolerated. There were no unintended effects of the treatment, and AEs were typical of those expected with the nasal application of CO_2. These local AEs were transient in nature, typically lasting during the 10-second administration only. There were no serious AEs, serious adverse device effects, or discontinuations due to AEs, and most reported AEs were mild or moderate in severity. The most frequently reported AE was nasal discomfort, which occurred more frequently among patients receiving active treatment and was considered related to study treatment.

The only severe AEs reported were nasal discomfort in 2 patients and dizziness and somnolence in 1 patient each. None of these resulted in discontinuation of the patients, and the patients continued to use the device for the rest of the study duration.

The short duration of nasal, noninhaled CO_2 application (10 seconds/nostril) is highly unlikely to lead to any systemic exposure to CO_2 and is therefore likely to be a local, physical effect. Previous *in vitro* studies have shown that a much longer duration (300 seconds) is needed to cause significant enough changes in pH that would lead to an effect on neurons and inhibit secretion of neuropeptides.[8]

The most commonly used pharmacological treatment for AR is oral antihistamines, with second-generation ones being more frequently used than first-generation ones mainly because of the significant sedation associated with the latter. Nasal antihistamines may have a faster onset of effect and have an effect on congestion. In general, though, antihistamines are not completely efficacious, are slow to act (usually 1 or more hours), and in higher doses many newer ones have associated sedation and most do not have a significant effect on congestion. Intranasal steroids work well against nasal and nonnasal symptoms of AR but have a slow onset of action, and there is a stigma associated with the use of steroids (even though systemic absorption with newer formulations is minimal).

Intranasal anticholinergics may have an effect on rhinorrhea, but not on other symptoms. Oral and topical decongestants may be used to treat congestion, but with regular use the former can cause irritability, palpitations, and insomnia and the latter rhinitis medicamentosa. In spite of the various treatments available, many patients with AR are not fully satisfied with their medications.[10] Thus, the utility of an as-needed treatment that rapidly improves all the principal symptoms of AR is significant.

CONCLUSIONS

SAR is an episodic disease with symptoms coinciding with exposure to allergens. Treatments available are usually administered on a scheduled basis (once a day, twice a day, etc.)—mostly because of the fact that these agents have a slow onset, and in some cases they work best when taken on a chronic basis. A possible exception is nasal decongestants, but these are limited by the sole effect on congestion and the potential for serious side effects such as rhinitis medicamentosa. What is needed is a rapidly acting treatment that provides significant

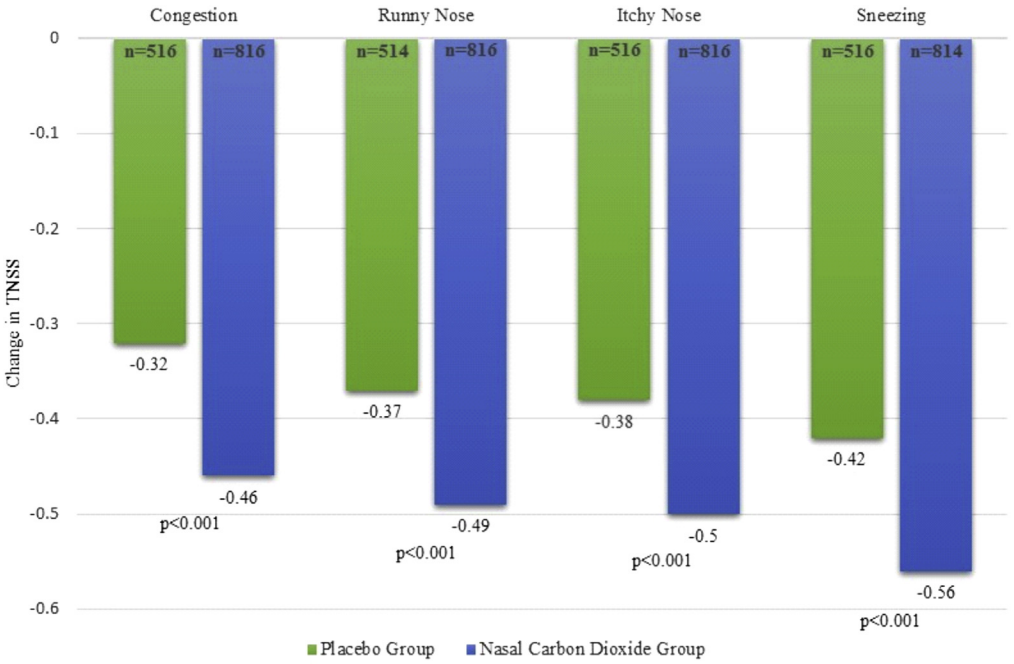

FIGURE 4. Change in individual nasal symptoms at 30 minutes (all assessments). *P* value for the change from baseline is from an analysis of covariance with baseline score (preuse TNSS) as a covariate.

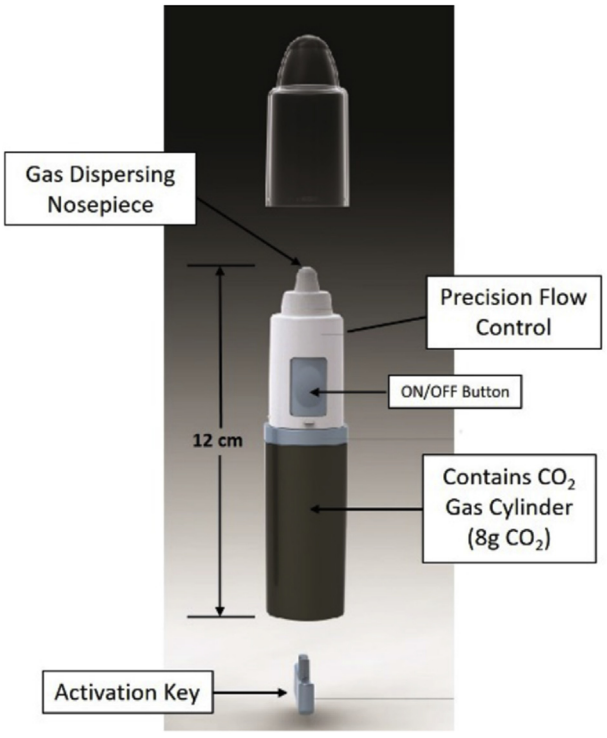

FIGURE 5. Current design of the nasal CO_2 device.

relief from all nasal symptoms. The nasal CO_2 device is effective for the as-needed treatment of all principal SAR symptoms. The effect is rapid and the effect size is large. It represents a novel potential option for the as-needed treatment of rhinitis symptoms (Figure 5).

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