International Journal of Innovative Research in Medical Science (IJIRMS)
Volume 11, Issue 01, January 2026,
*https://doi.org/10.23958/ijirms/vol11-i01/2155*

**Original Article**

# Safety of Nebulization with a Super-Oxidized Solution in Healthcare Personnel Exposed to COVID-19

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Received: 23 December 2025; Accepted: 07 January 2026; Published: 10 January 2026

## Abstract

This study presents a case series conducted at a private hospital in Mexico City, where healthcare personnel were exposed to SARS-CoV-2 without adequate protective measures. As a voluntary prophylactic measure, and given the high mortality from COVID-19 at that time, a protocol was implemented consisting of nebulization with a super-oxidized solution (Microdacyn) for 15 minutes, three times daily for 7 days. The objective was to evaluate the safety of this preventive treatment. Specific measurements were obtained in each participant to demonstrate the safety of the procedure. Of eleven initial subjects, eight completed the protocol; one was excluded due to pre-existing cardiac arrhythmia and two were withdrawn for other reasons (one subject had a positive SARS-CoV-2 PCR test, with adequate oxygen saturation and no complications, and another withdrew consent). The mean age of participants was 33.2 years, with three women and five men. The protocol was initiated on the fourth day after exposure. At baseline and at the end of the protocol, SARS-CoV-2 PCR testing, IgG and IgM antibodies, chest radiographs, general blood tests, and spirometry were performed. Positive IgG was found in two subjects who reported symptoms consistent with COVID-19 months earlier. No serious or clinically significant adverse events were reported during treatment; no changes were observed in vital parameters (heart rate, respiratory rate, oxygen saturation), and there were no hospital admissions or deaths. At the end of the protocol, all patients were negative for SARS-CoV-2 by PCR, spirometry did not differ from baseline, and the remaining laboratory and imaging studies showed no significant changes. These results suggest that nebulization with a super-oxidized solution is safe as a prophylactic treatment in individuals at high risk of exposure to SARS-CoV-2, which could serve as a precedent for the management of this and other types of respiratory infections.

**Keywords:** ***SARS-CoV-2, ultrasonic nebulization, super-oxidized solution, prophylaxis, healthcare personnel, spirometry, safety, harmlessness.***

## Introduction

The COVID-19 pandemic had a major global impact due to the high transmissibility of the disease and its wide range of clinical manifestations, from mild to severe [1]. When this study was designed and conducted, Mexico City was at the highest epidemiologic alert level due to poor adherence to preventive measures in the general population (January 2021), with limited hospital bed availability, scarce medical resources in staff and equipment relative to demand, and very high mortality due to extreme transmission. Patients with severe disease (requiring supplemental oxygen, invasive mechanical ventilation, and intensive care support) [2] in our country, and depending on age group, had mortality rates reaching half or more of cases. Estimated mortality at the time of the study was slightly above 8%, males accounted for 63.3% of deaths, and the predominant group was between 40 and 80 years of age [3].

Vaccination at that time was still limited, although it later mitigated the impact of COVID-19 [4]. According to current guidelines, population-level protection today depends mainly on vaccination, antivirals, and control measures [1].

Virus transmission occurs primarily through the airborne route. The virus reaches the host directly at the airway epithelium (mouth, nose, throat, trachea, and lungs) through inhalation or contact with respiratory droplets expelled when speaking, spitting, coughing, or sneezing by infected individuals [5]. The accessibility and large surface area of the airways-especially the lungs-contribute to infectious susceptibility. However, these same characteristics provide a unique opportunity for topical therapy in the form of respiratory aerosols. An aerosol or aerosolization of a solution is the suspension of very fine liquid droplets traveling in a gas, which allows diffusion and access to proximal and distal airways independent of respiratory mechanics [6,7].

Antiseptics are defined as biocidal substances that destroy or inhibit the growth of microorganisms within or on living tissue and ideally do not cause damage to the organism [8]. This group

includes neutral-pH electrolyzed super-oxidized solutions (SOS; superoxidized solutions) [9-11]. One production method is electrolysis (separation of elements in a compound using electricity) of sodium chloride solution. The process yields concentrations in the range of 80 parts per million (ppm) of available chlorine concentration (ACC), approximately 0.0023% hypochlorous acid (HOCl; contributing ~40 ppm ACC) and 0.0008% sodium hypochlorite (NaOCl; contributing ~40 ppm ACC), and very small amounts of other reactive oxygen species such as sodium dioxide and hydrogen peroxide [12]. These solutions constitute a potent oxidizing system (HOCl/OCl−) under physiological conditions (E0 '= +1.48 V for HOCl; E0 '= +0.9 for OCl−),[13] conferring broad-spectrum efficacy against viruses, bacteria, yeasts, and bacterial spores [10,14,15]. HOCl is the species with the greatest antimicrobial effect and highest concentration between pH 5 and 7.5.

The main mechanism of action on viruses is oxidative, producing hydroxyl free radicals (–OH) that inactivate proteins (e.g., by substituting exposed sulfhydryl groups), particularly surface proteins on the viral envelope, inactivate viral enzymes, or destroy viral nucleic acid, collectively eliminating infectivity. Viral inactivation begins within 15 seconds, achieving more than a 3 log10 reduction in viral concentration by 30 seconds [16]. This effect has been demonstrated in members of the coronavirus family such as SARS-CoV-2 [17-19]. Although numerous studies show that SOS at the concentrations described do not have negative effects in cellular tissues [20] or animals, [14,21] there are still few studies in humans.

SOS have low cytotoxicity (in vitro tissue studies and animal studies) in oral and respiratory mucosa models at concentrations ≤300 ppm with brief exposures; the risk of cellular and genetic damage may occur at higher concentrations or with prolonged exposures [22-24]. These studies indicate that safety depends on concentration, contact time, and the specific formulation [20,25]. There are few clinical studies in humans assessing mucosal safety; results show an almost null effect, and we found no phase II studies of SOS nebulization into the airways. During the 2019 pandemic, some studies were conducted using nebulized SOS in humans [26,27].

From the perspective of an experimental prophylactic alternative based on the concept that SOS nebulized into the airway could act during the viral phase at the respiratory epithelium (from nasopharyngeal epithelium to pulmonary epithelium), decreasing viral load on the epithelial surface [28,29]–a group of healthcare workers exposed without respiratory protection to a patient with severe COVID-19 were invited to participate voluntarily. This is the first human study focused on the safety of SOS as an antiseptic on the respiratory surface beyond the upper airway mucosa.

## Materials and Methods

At a time when the COVID-19 pandemic was at one of its highest peaks of contagion (and with higher mortality) in Mexico, a group of healthcare personnel at a private hospital in Mexico City provided care–without specific protective equipment to prevent contact with airway secretions to a patient with severe COVID-19 in an emergency situation. After exposure (Day 0), they were invited to participate in this study as volunteers. The proposed intervention consisted of 15-minute nebulizations with an SOS (Microdacyn solution, patented in Mexico by Invekra, S.A.P.I. de C.V. with numbers 304152, 304153) three times daily for 7 days. In the pandemic context, a prior case series using this intervention had shown favorable clinical outcomes without major adverse events and minimal, well-tolerated minor events [26]. The expected benefit for this group was a prophylactic effect to prevent disease acquisition.

The day after exposure to the index patient (Day 1), an informational meeting was held to explain objectives, procedures, potential benefits, and possible risks, both related to the product (Microdacyn solution™ [SOS]) and the nebulization procedure, emphasizing that although the product is a well-known antiseptic with biocidal effects, there is limited documented evidence for its nebulized use intended to reach the pulmonary epithelium, and thus this route of administration was experimental. Warning signs and probable adverse effects were explained, along with an emergency response manual and how to request healthcare services if any new symptom occurred, whether or not considered an adverse event. It was explained that application and daily follow-up would be carried out under direct supervision in each session by at least one of the investigators for 7 consecutive days, and that participants could contact the team 24/7 for any concern during the study or any subsequent event potentially related to exposure to the product or the intervention for up to one month after the final nebulization; participants were also encouraged to express any ethical concerns.

After the explanatory session, sufficient time was provided for questions to ensure full understanding. In private with each subject and a family member, the informed consent was read, summarized, and questions were addressed before signing. Consent was obtained voluntarily and without pressure; participants could revoke consent at any time without repercussions and without losing follow-up during the study and for up to one month afterwards.

Personal data protection was ensured by assigning a unique, non-reproducible code instead of using real names. This code was used in all databases and data collection forms to keep participant information anonymous. The master list linking identification codes to real names was stored in a separate secured file accessible only to the principal investigator. Data were stored in encrypted digital files with secure credentials; access was restricted to essential study personnel who were bound by strict confidentiality standards and signed non-disclosure agreements. Printed documentation was stored in locked filing cabinets in a secure location accessible only to authorized personnel.

All 11 exposed healthcare workers agreed to participate. Subjects were adults over 18 years of age of both sexes; women of childbearing age (18-40 years) were not pregnant (negative pregnancy test prior to protocol initiation). Pre-exposure screening confirmed no fever and/or respiratory symptoms during the 5 days prior to exposure to the index patient. Exclusion criteria included: subjects who had received hospital care within one month prior to the day of exposure; subjects or family members who did not accept the management protocol or did not provide consent. Elimination criteria included withdrawal of consent at any time after initial consent, refusal to cooperate with follow-up, or discontinuation of treatment.

The day after the general session and individual consent process (Day 2), clinical assessment was performed to determine current health status. Baseline laboratory and imaging studies included: chest X-ray (PA view), electrocardiogram, complete blood count, comprehensive metabolic panel (35-item chemistry), D-dimer, ferritin, C-reactive protein, pregnancy test (female subjects), oropharyngeal swab for SARS-CoV-2 PCR, and spirometry. A positive SARS-CoV-2 test was a criterion for exclusion/elimination. The same studies were obtained at the end of the 7-day nebulization period as systemic safety parameters after treatment, and spirometry was repeated on Day 8; final spirometry was performed on Day 9, two days after completing treatment.

Nebulization began on the night of Day 3 after exposure to the index patient, after baseline clinical, laboratory, and imaging evaluation had been completed for each subject. Nebulization was

administered using a mesh ultrasonic nebulizer; each subject received a dedicated device. Five milliliters of the super-oxidized solution were placed in the nebulizer reservoir. Nebulization lasted 15 minutes and was administered every eight hours for 7 days (21 applications total). The mesh ultrasonic nebulizer generates droplet diameters of 1–5 µm, allowing diffusion to the pulmonary epithelium independent of ventilatory mechanics.

In-person monitoring was performed by one or more investigators during each nebulization session for each subject. The monitor completed a paper clinical log documenting study variables. Clinical recording was performed before and after each of the three daily nebulizations for 7 days (21 applications). Each nebulization session was performed in an isolated and well-ventilated environment.

The main variables used to compare the immediate effect of nebulizations were vital signs: oxygen saturation ($SpO_2$) and heart rate (HR) by pulse oximetry; temperature by infrared thermometer; respiratory rate (RR; visual count of respiratory movements in one minute); blood pressure (BP; manual sphygmomanometer and stethoscope). These were recorded daily before and immediately after each nebulization. Any adverse event occurring during nebulization, within 10 minutes after the session, and whether the event was severe enough to require discontinuation were also recorded.

A scoring system was established for each vital parameter monitored before, during (only if clinical distress was observed), and after treatment. The clinical monitor (investigator) recorded the presence or absence of any adverse event or abnormality observed, classified according to the predefined scoring system and correlated with the treatment protocol to facilitate early risk identification, reinforce safety measures, and predefine response/action pathways to correct causes. These systems also served to support validity and reliability of the study findings. Scoring systems were defined as follows:

1. Adverse Event Assessment System. Classification of adverse events by severity: Mild (Grade 1): events not requiring medical treatment and not interrupting the study. Moderate (Grade 2): events requiring medical treatment but not resulting in study interruption. Severe (Grade 3): events requiring hospitalization, surgical intervention, or causing persistent disability. Life-threatening (Grade 4): events that endanger the subject's life and require intensive medical care. Death (Grade 5): events resulting in death. Causality relationship: Positive: clearly attributable to treatment. Indeterminate: cannot be confirmed as related or unrelated. Negative: clearly not related to treatment.
2. Normality/Abnormality Assessment System for Vital Parameters. For each parameter (HR, $SpO_2$, RR, BP, temperature), reference ranges and recommended actions were established, in addition to discontinuing nebulization.
    - Heart rate: Normal 60–100 bpm. Abnormal: bradycardia <60 bpm (consider abnormal if persistent); tachycardia >100 bpm (requires evaluation).
    - Oxygen saturation: Normal 95–100%. Abnormal: mild hypoxemia 90–94%; moderate 80–89% (requires immediate evaluation); severe <80% (requires urgent medical intervention).
    - Respiratory rate: Normal 12–20 breaths/min. Abnormal: bradypnea <12 (evaluate causes); tachypnea >20 (requires evaluation).
    - Blood pressure: Normal 90–139/60–80 mmHg. Abnormal: hypotension <90/<60 (immediate evaluation, place patient supine); hypertension >140/>90 (consider follow-up); >160/>100 (administer sublingual antihypertensive, recheck BP at 15 min with constant clinical evaluation).
    - Temperature: Normal 36.1–37.5°C. Abnormal >37.5°C; febrile >38.2°C (evaluate causes; obtain blood/urine tests and chest radiograph); hypothermia <36.1°C (evaluate causes).

Primary variables to evaluate whether the treatment period induced changes in respiratory function were spirometry parameters: forced expiratory volume in one second ($FEV_1$), forced vital capacity (FVC), and the $FEV_1$/FVC ratio. Final spirometry was performed on Day 9, two days after completion of treatment.

**Statistical analysis:** Descriptive statistics were used for demographic analysis. Given the design and small sample size, Fisher's exact test was selected as the standard method for bivariate analysis of dichotomous variables (normal vs abnormal) of vital signs. Additionally, pre- and post-nebulization comparisons for repeated measures were analyzed using descriptive statistics (mean, SD, SEM, 95% CI) for each variable, paired Student's t-test (post vs pre) and Wilcoxon test (nonparametric) for each variable, as well as a mixed-effects model with each subject as a random effect (intercept) and time (pre/post) as a fixed effect-corresponding to a repeated-measures ANOVA more suitable for within-subject repeated data.

For spirometry outcome comparisons, $FEV_1$, FVC, and $FEV_1$/FVC were analyzed in absolute values (liters and percentage) and as percent predicted (GLI-adjusted). Normality of pre-post differences was assessed using the Shapiro–Wilk test. Since in all cases $p>0.05$ and normality could not be rejected, paired Student's t-test was used to compare means before vs after. As an additional nonparametric contrast, the Wilcoxon signed-rank test was also calculated.

## Results

In this case series, 11 patients were enrolled; one was excluded and two were withdrawn. The protocol was completed by 8 subjects with a mean age of 33.2 years: 2 female and 6 male. All were apparently healthy, without relevant medical history. In the excluded subject, a cardiac arrhythmia was identified on electrocardiogram, and the subject was referred to cardiology for continued management. Two subjects were withdrawn: one with a positive rapid SARS-CoV-2 test on baseline assessment, and another who reported headache after the first nebulization session and therefore withdrew informed consent.

Except for the subject with arrhythmia and the subject positive for COVID-19, the remaining baseline laboratory and imaging studies were clinically unremarkable. However, on baseline spirometry, one patient showed a mild restrictive pattern (77% predicted $FEV_1$ and 88% predicted FVC) and was not excluded. Two patients were excluded from spirometry analysis due to technical failures (unsatisfactory spirometry tests). The remaining spirometry tests were generally quality grade B or A, considered adequate maneuvers, and were interpreted as normal.

During nebulization, aside from the headache that led one subject to discontinue participation, no severe adverse events occurred. Minor adverse events reported included nasal discharge, mild nasal burning sensation, sneezing, or mild cough during nebulization and occasionally immediately after. No suspension or modification of nebulization was required when these minor adverse events occurred. Minor adverse events were classified as mild (Grade 1: events not requiring medical treatment and not interrupting the study) and clearly attributable to treatment. There were no occasions during or after nebulization in which abnormal changes occurred in vital signs (RR, HR, $SpO_2$, temperature, BP) during the seven days of administration.

**Table 1: Mean heart rate (HR; beats per minute: bpm), respiratory rate (RR; breaths per minute: brpm), and oxygen saturation ($SpO_2$), along with the standard deviation (SD), mean difference, 95% confidence interval (95% CI), and p-value.**

| Variable | Media PRE (±DE) | Media POST (±DE) | Dif. media | 95% IC | p-valor |
|---|---|---|---|---|---|
| FC (lpm) | 77.5 ± 5.7 | 79.4 ± 6.4 | 1.9 | 0.2 a 3.5 | 0.03 |
| FR (rpm) | 17.8 ± 0.7 | 18.1 ± 0.7 | 0.3 | 0.1 a 0.6 | 0.01 |
| $SO_2$ (%) | 95.5 ± 0.6 | 95.7 ± 0.8 | 0.3 | −0.1 a 0.6 | 0.14 |

At the end of the 7-day nebulization protocol, a total of 168 measurements were obtained for each vital sign (8 subjects with 21 applications each). Although no clinically relevant differences were identified, parametric comparisons were performed between pre- and post-application values across the 21 sessions for HR, RR, and $SpO_2$. Table 1 shows increases in HR (+2 bpm) and RR (+0.3 breaths/min) that were statistically significant; however, the magnitude was minimal and not clinically relevant. $SpO_2$ remained stable within normal values (95–98%), with no clinically relevant or statistically significant differences. This pattern was consistent in the combined analysis (169 pre/post measurements; not shown) and in the per-patient analysis (21 paired pre/post measurements, 8 patients; Table 1). Figure 1 shows the graphs of HR, RR, and $SpO_2$.

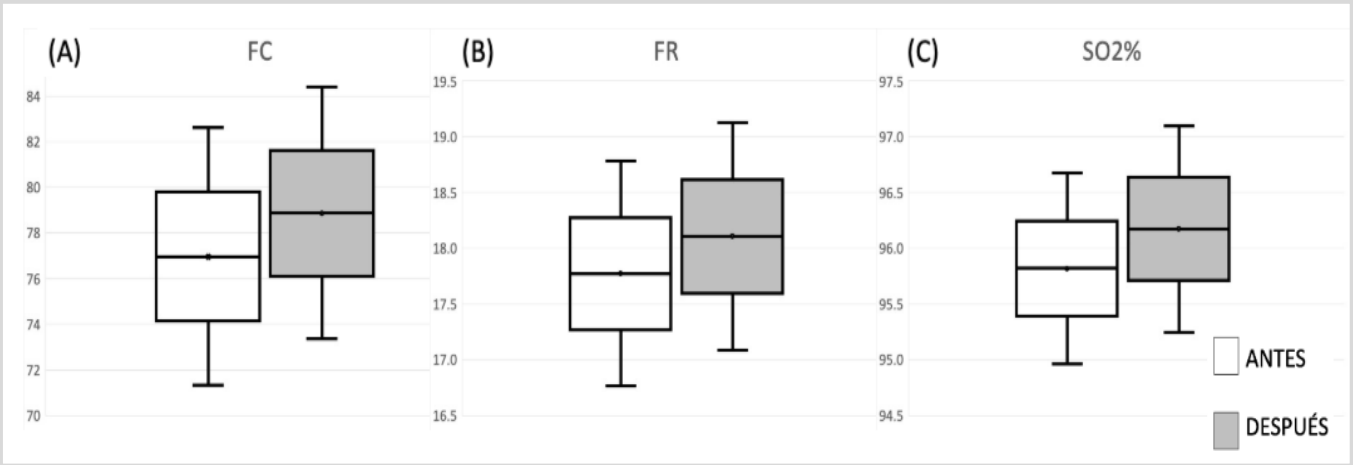


**Figure 1: Plots of the means (±95% CI; n = 168 measurements before and after each nebulization) of: (A) Heart rate (FC), (B) Respiratory rate (FR), and (C) Oxygen saturation ($SpO_2$). (A) The mean difference between post- and pre-nebulization measurements was small (≈ +0.29 bpm); paired t-test p ≈ 0.068, and the mixed-effects model estimated a time-effect coefficient of +0.286 (p ≈ 0.068). (B) Likewise, for respiratory rate (no significant differences were detected between PRE and POST by either the paired t-test or the mixed-effects model), nor for (C) $SpO_2$ (PRE and POST means remained within normal ranges, ≈95–97%, and no significant differences were observed).**

When comparing laboratory and imaging studies before and after the nebulization period, there were no clinically relevant or statistically significant differences.

Table 2 shows that mean $FEV_1$ and FVC (liters) were virtually identical before and after treatment (p=0.435 and p=0.650, respectively). The $FEV_1$/FVC ratio (%) increased slightly (83.8% pre vs 85.7% post), but this difference was not significant (p=0.203). Similarly, in the % predicted section, predicted percentages for $FEV_1$, FVC, and $FEV_1$/FVC showed non-significant variations (e.g., $FEV_1$: 104.6% pre vs 101.1% post, p=0.461; $FEV_1$/FVC: 99.4% pre vs 102.7% post, p=0.069). In all cases p>0.05 (paired t-test), indicating no statistically significant differences. The Wilcoxon test yielded similar p-values and also confirmed the lack of significant changes (not shown). Figure 2 shows graphs of these data.

**Table 2: Descriptive statistics of $FEV_1$, FVC, and $FEV_1$/FVC (absolute values and percent predicted values: % predicted) before and after Microdacyn treatment (n = 6). Mean (±SD), median, and paired t-test p-value are included.**

| Variable | Antes | | Después | | p-valor |
|---|---|---|---|---|---|
| | Media (±DE) | Mediana | Media (±DE) | Mediana | |
| FEV1 (L) | 3.6 ± 0.4 | 3.4 | 3.5 ± 0.6 | 3.3 | 0.435 |
| FVC (L) | 4.3 ± 0.4 | 4.3 | 4.1 ± 0.6 | 4.2 | 0.65 |
| FEV1/FVC (%) | 83.8 ± 4.2 | 83 | 85.7 ± 4.4 | 85 | 0.203 |
| **% Predictivo** | | | | | |
| FEV1 (%) | 104.6 ± 12.4 | 105.9 | 101.1 ± 15.2 | 101.5 | 0.461 |
| FVC (%) | 104.9 ± 9.5 | 106.4 | 98.2 ± 14.0 | 98.9 | 0.143 |
| FEV1/FVC (%) | 99.4 ± 5.9 | 98.8 | 102.7 ± 4.8 | 101.5 | 0.069 |

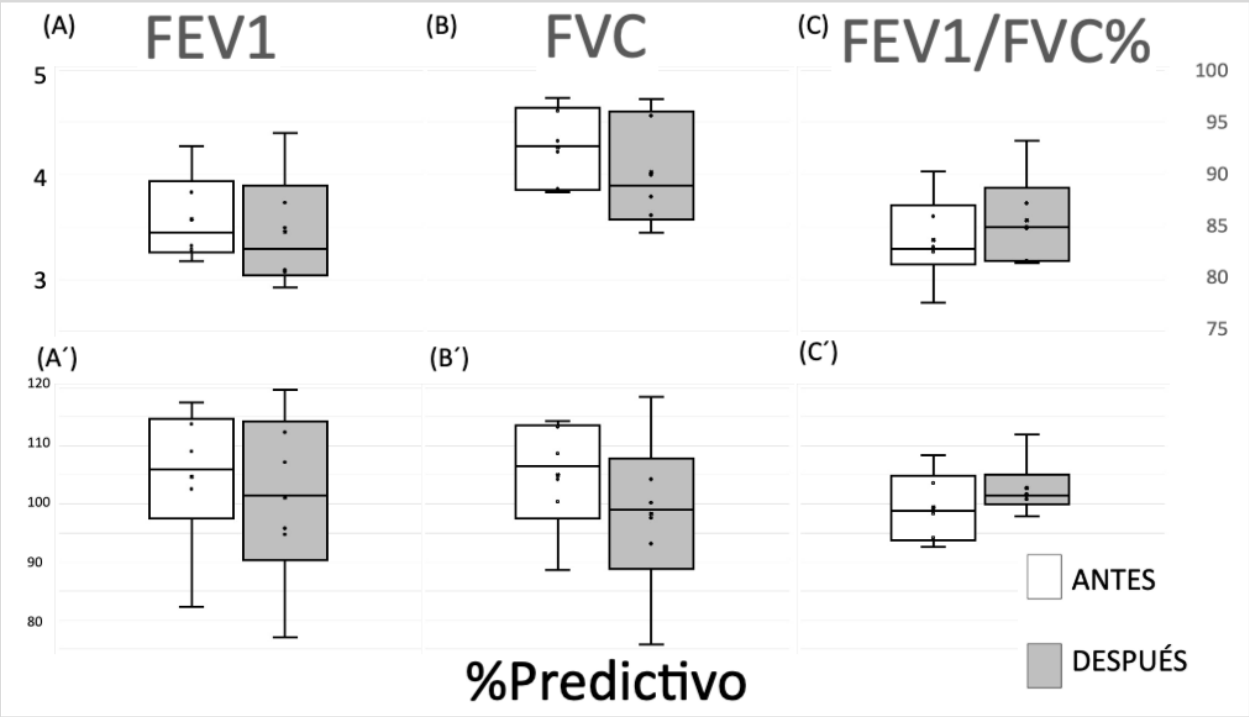


**Figure 2: Box-and-whisker plots of measurements from the 6 exposed subjects before and after nebulizations (7 days) of: (A) Forced expiratory volume in 1 second ($FEV_1$; L), (B) Forced vital capacity (FVC; L), and (C) the $FEV_1$/FVC ratio expressed as a percentage ($FEV_1$/FVC%). Plots (A′), (B′), and (C′) show the corresponding percent predicted values for $FEV_1$, FVC, and $FEV_1$/FVC, respectively. Percent predicted values were obtained using the online GLI Lung Function Calculator, accounting for sex, age, height, and other ethnicities.**

**Table 3: Spirometry results before and after the exposure period (5 mL of nebulized Microdacyn for 15 min, every 8 h, three times daily, for 7 days; n = 6 subjects). Percent predicted values were obtained using the online GLI Lung Function Calculator, accounting for sex, age, height, and other ethnicities.**

| | | | | FEV1 (L) | | | | FVC (L) | | | | FEV1/FVC (%) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Paciente | Edad | Sexo | Estatura | ANTES | | DESPUÉS | | ANTES | | DESPUÉS | | ANTES | | DESPUÉS | |
| # | (años) | | (cm) | L | %Pred | L | %Pred | L | %Pred | L | %Pred | L | %Pred | L | %Pred |
| 1 | 30 | M | 174 | 3.28 | 82.3 | 3.07 | 77.0 | 4.22 | 88.6 | 3.61 | 75.8 | 77.7 | 92.6 | 85.0 | 101.3 |
| 2 | 52 | M | 170 | 3.83 | 117.4 | 3.09 | 94.7 | 4.61 | 113.2 | 3.79 | 93.1 | 83.1 | 103.6 | 81.5 | 101.7 |
| 3 | 33 | M | 165 | 3.57 | 102.5 | 3.73 | 107.1 | 4.32 | 104.2 | 4.56 | 104.2 | 82.6 | 98.3 | 81.7 | 102.7 |
| 4 | 33 | M | 174 | 4.27 | 109.0 | 4.4 | 112.3 | 4.73 | 100.4 | 4.72 | 100.2 | 90.3 | 108.3 | 93.2 | 111.9 |
| 5 | 28 | F | 160 | 3.32 | 113.7 | 3.49 | 119.6 | 3.86 | 114.2 | 4.0 | 118.4 | 86.0 | 99.3 | 87.6 | 100.7 |
| 6 | 27 | F | 163 | 3.17 | 102.7 | 2.92 | 95.8 | 3.83 | 108.6 | 3.44 | 97.6 | 82.8 | 94.2 | 84.9 | 97.8 |

## Discussion

Nebulizations with SOS (Microdacyn 60, 5 mL for 15 min, three times daily × 7 days; 21 applications per patient; 168 applications total across 8 subjects) are safe from a clinical, hemodynamic, and respiratory standpoint.

In this set of observations, nebulization did not show clinically relevant changes during or after application; it did not show statistically significant or clinically relevant immediate pre/post changes in HR, RR, or $SpO_2$; and it did not show changes in spirometry before and after 7 days of nebulization administered three times daily. These findings support the safety of the nebulized substance with respect to the vital parameters measured during the sessions. Clinical surveillance is nonetheless recommended in studies with larger sample sizes or in high-risk populations to confirm these results.

The COVID-19 pandemic more frequently affected and had worse prognosis in older individuals and those with chronic degenerative comorbidities [30]. However, it also steadily increased the number of young patients and infected healthcare workers [31]. In Mexico, high viral transmissibility, insufficient healthcare infrastructure, widespread poor adherence to preventive measures, and high prevalence of metabolic syndrome translated into higher risks of hospitalization and mortality than globally reported,[32]. reaching figures up to 11% of cases. To date, there is no specific treatment considered the gold standard for COVID-19 [33]. Many drugs and therapies initially considered promising later showed little benefit or even contraindications [34].

It is now known that SARS-CoV-2 initially replicates in the nasal and oropharyngeal mucosa during the first days of infection (viral phase, ~4 days) and later in the lower airway (pulmonary phase) [35,36]. Transmission by infected individuals without symptoms (presymptomatic or persistently asymptomatic) was decisive for the epidemic curve in the general population and among healthcare personnel [36].

In the present case series, triggered by exposure to a patient admitted to the emergency department for life-threatening penetrating abdominal trauma who tested positive for COVID-19 in the immediate postoperative period, the healthcare team was at high risk of infection due to advanced airway procedures and intubation.

Under this risk, this group was offered prophylaxis via SOS nebulization, a technique evaluated as adjunct treatment in COVID (+) patients and, in that context, associated with clinical improvement without increased mortality [26]. The use of SOS as a topical agent with high virucidal activity administered by nebulization to the respiratory epithelium is an experimental strategy, and at the time of the study there was limited scientific information on inhalation toxicity at concentrations contained in commercial SOS (80 ppm FAC). Nevertheless, clinical observations from our own use as prophylactic and therapeutic measures, and observations in the prior patient series and many other patients, encouraged development of this protocol both as a preventive measure for exposed subjects and as an opportunity to obtain reliable inhalation safety data on the respiratory epithelium and respiratory function in general.

The safety of the SOS used in this study in the airways can be described in three domains: (a) clinically, due to scarce mucosal irritation manifestations that never required discontinuation; (b) physiologically, due to small changes without clinical or statistical significance in RR, HR, and $SpO_2$; and (c) functionally, due to absence of spirometry changes at baseline and after 7 days of nebulization three times daily. In vitro and in vivo studies assessing SOS safety/toxicity generally show an excellent concentration- and exposure time-dependent safety margin. A concentration range considered acceptable to avoid toxicity is below 300 ppm. Lewandowski et al. demonstrated that repeated exposures to aerosolized HOCl at concentrations above 300 ppm may induce cytotoxicity and genotoxicity in human fibroblasts, whereas brief exposures (3 min) at 300 ppm did not cause significant damage [23]. Kim et al. showed that nasal irrigation for up to 2 hours with low-concentration HOCl (3.5 ppm) did not show cytotoxicity in human nasal epithelial cells, nor were morphological alterations observed [37]. Likewise, Aras et al., after intraperitoneal infusion of neutral-pH SOS in rats with single and multiple applications, did not observe histopathologic changes in coelomic cells of the abdominal wall, intestinal, or hepatic tissues [38]. Both studies suggest a favorable safety profile after topical use on mucosa and serosa. Regarding lower airway exposure, Benedusi et al. evaluated the safety of nebulized HOCl (300 ppm) in 2D and 3D models of human lung tissue and did not observe adverse effects on viability or tissue morphology, supporting safety at moderate concentrations in situ.[22] Conversely, Murashevych et al. conducted in vivo studies in rats exposed by inhalation to gaseous HOCl (2.0 and 5.0 $mg/m^3$, approximately 1 and 2.3 ppm) for 4 hours, showing no mortality or significant alterations in hematologic, biochemical, or pulmonary histopathologic parameters over 14 days of follow-up; transient changes in antioxidant enzyme activity were detected at 5 $mg/m^3$, particularly in older animals [39]. These findings suggest that under controlled conditions and at concentrations similar to those used in environmental disinfection, inhaled HOCl has low acute toxicity risk in animal models. Relevant toxic effects have not been reported in in situ and in vivo models under these conditions, though caution is recommended with high concentrations or prolonged exposures.

In addition to these studies, super-oxidized solutions have been used topically in humans for more than two decades across multiple clinical scenarios–from skin surfaces to cavities such as the mediastinum and peritoneum–primarily in infectious settings, with a good safety profile [40-53].

There is currently sufficient evidence to explore new inhalation strategies through human studies to demonstrate the safety and efficacy of SOS as treatment and prophylaxis for known infectious diseases of the airways, and potentially for future viral infections [14,54].

## Declarations

## Conflicts of Interest

Dr. Rebollar González, has participated as a speaker for Sanfer, the company that commercializes the Microdacyn solution used in this study. We explicitly declare that Sanfer did not provide any funding for this study. Funding for all laboratory tests, imaging studies, and spirometry, as well as mesh nebulizers, Microdacyn solution bottles, and clinical areas where the study was conducted, was covered by Hospital Boutique Riobamba. Remaining costs (other supplies, logistical support, monitoring) were covered by the investigators. The hospital, as study sponsor, did not influence study design, data collection and analysis, manuscript preparation, or the decision to publish results. The research team maintains a firm commitment to objectivity and scientific integrity. Measures were taken to ensure that the relationship with Sanfer or the hospital did not compromise study impartiality. We clearly express our commitment to transparency; all information regarding potential conflicts of interest has been fully disclosed as required by scientific publication standards, ensuring maximum transparency for the reader.

## Ethical Considerations

In the context of the epidemiologic emergency and the absence of routine activity due to contingency and lockdown measures by the host hospital's research ethics committee, rapid implementation of measures was crucial to respond to the pandemic crisis. Together with hospital authorities, the director, and the administrative board, we considered the need to act quickly to address an unprecedented urgent clinical problem during the COVID-19 outbreak, and agreed that the proposed protocol could have a significant impact on crisis management, justifying proceeding without prior conventional research ethics committee review. Nevertheless, all guidelines for adherence to ethical principles were followed. Although ethics committee approval was not obtained due to the circumstances, the principles of the Declaration of Helsinki were followed, including prioritization of participant welfare and rights, obtaining informed consent, ensuring risks were reasonable in relation to expected benefits, and adherence to International Conference on Harmonisation Good Clinical Practice (ICH-GCP) standards, ensuring that study design, execution, and documentation met quality and ethical standards.

## Data Availability

The data support the findings of this study are available from the corresponding author, [RCRG], upon reasonable request.

## List of Abbreviations

**ACC**: available chlorine concentration
**ANOVA**: analysis of variance
**Bpm**: beats per minute
**BP**: blood pressure
**Brpm**: breaths per minute
**CDMX**: Mexico City
**CI (95% CI)**: (95%) confidence interval
**E0'**: standard reduction potential
**FC**: Heart rate
**$FEV_1$**: Forced expiratory volume in 1 second

**FR**L Respiratory rate
**FVC**: Forced vital capacity
**GLI**: GLI Lung Function Calculator
**HOCl**: Hypochlorous acid
**HR**: Heart rate
**ICH-GCP**: International Conference on Harmonisation Good Clinical Practice
**IgG**: Immunoglobulin G
**IgM**: Immunoglobulin M
**NaOCl**: Sodium hypochlorite
**OCl⁻**: Hypochlorite
**PA (view)**: Posteroanterior view
**PCR**: Polymerase chain reaction
**Ppm**: Parts per million
**RR**: Respiratory rate
**SARS-CoV-2**: Severe acute respiratory syndrome coronavirus 2
**SD**: Standard deviation
**SEM**: standard error of the mean
**SOS**: Super-oxidized solutions
**$SpO_2$**: Oxygen saturation
**⁻OH**: hydroxyl free radical(s)

## Author Contribution Statement

All authors collaboration played either leadership or significant supporting roles in one or more of: the management, development, data analysis and preparation of this manuscript.

## Acknowledgments

This research was supported by Hospital Boutique Riobamba CDMX. Special thanks to the entire hospital team involved.

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