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Severe SARS-Cov-2 Co-Adjuvant Treatment with Ethanol Nebulizations: Report of Three Cases with Good Outcomes

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1. Abstract

1.1. Objective: We report the retrospective analysis of three patients with severe COVID-19, with a SpO2 of 87% on average, treated with a co-adjuvant therapy of inhaled ethanol, as well as a review on the use of this therapy in some respiratory diseases.

1.2. Method: The treatment was 20% nebulized ethanol, 10 minutes, TID, in addition to the standard anti-COVID-19 therapy on that time. Treated patients were compared against five contemporary controls also with SARS-COV-2 with similar clinic characteristics, but without ethanol therapy. We also made a bibliographical review and a survey to MDs with experience in this, not so common, therapy.

1.3. Results: The co-adjuvant treatment displayed good outcomes: decreased dyspnea, increased 5% of SpO2 after the inhalation session, enhanced sleep quality and decreased the mid and long-term sequelae. We compare our results with two recent reports on clinical phase II protocols of similar inhaled ethanol co-adjuvant treatments against COVID-19 one with good and one with negative outcomes.

1.4. Conclusions: The present study tips the scale toward the good outcomes, and complements information from those works, it finds an experience for more than 70 years on this therapy; it reviews the only risk of this treatment, a possible mild alcohol-induced asthma in some asthmatic patients, which is easily avoided by excluding patients with these precedents. The present treatment still needs a phase II protocol in order to confirm results, but all these precedents strongly suggest a very low toxicity with a clear beneficial use.

2. Introduction

The absence of specific and affordable therapies against COVID-19 at the beginning of the pandemic significantly increased the lethality and spread of the disease, creating a global humanitarian, social, and economic crisis that was perhaps the worst global emergency since the Second World War [1].

Although the invention of vaccines in 2021 significantly reduced the dimensions of the SARS-Cov-2 pandemic (severe acute respi-

ratory syndrome coronavirus 2), as well as its mortality, all data suggest that the virus will persist in a more endemic form [2], or in an even more complex challenge, such as the high index of virus mutation [3]. These factors urge us to continue researching possible alternative therapies against this virus.

The antiseptic use of ethanol was discovered more than 150 years ago, as an antiseptic in surgery through the application of alcoholic drinkable spirits [4]; its specific anti-coronavirus effect was first described in 2005 in relation to SARS-Cov-1 [5], which was later corroborated during the SARS-Cov-2 pandemic, with its universal use as an antiseptic, even with low concentrations of alcohol [6].

Since the beginning of the pandemic two theoretical reports suggested that inhaled ethanol could be used as antiseptic in health workers exposed to COVID-19 [7], or as a possible treatment for asymptomatic SARS-CoV-2 patients [8]. Subsequently, two phase II clinical experiments with inhaled ethanol treatment protocol against SARS-CoV-2: one at the Universidad de Santiago de Compostela in Spain [9], and the other at Mansoura University in Egypt [10].

2.1. Precedents of Ethanol Therapy for Other Respiratory Diseases

Inhaled ethanol has been widely used as treatment against acute pulmonary edema from the 1950s, [11,12], although this use declined since the 1980s, when ethanol was displaced by acetylcysteine as anti-foaming drug [13, 14]. The first protocol against pulmonary edema used a very high dose of alcohol: 96% for 30 minutes [15]. This dose can be irritating, but in 2012 Qiujiao showed that concentrations between 15 to 25% displayed better tolerance and maintained its effect against pulmonary edema [11].

Previously, one of the authors of the present work (F. Alejandro Montaño-Jiménez) had used this treatment in pediatric patients with croup (severe laryngotracheitis), under the assumption that this treatment was systematically applied in Mexican hospitals. However, there are no bibliographic reports on its use in this context. To further investigate this treatment, we searched among five medical associations, and found six MDs with experience on this treatment and conducted targeted interviews with them.

2.2. Risks of Using Ethanol in the Respiratory Tract

It is known that high doses of inhaled ethanol can impair mucociliary clearance, while a low dose can be beneficial: it causes broncho-dilatation, attenuates airway inflammation, and enhances ciliary clearance [16]. The only risk reported for inhaled ethanol is a mild bronchial constriction in some asthmatic patients, referred to as alcohol-induced asthma (AIA), and reported since 1981 [17]. Oral AIA is activated in less than 15 minutes, of a moderate severity and less than one hour lasting. Interestingly, it is reported that inhaled alcohol activates even milder bronchospasms than oral ingestion [18]. Asthmatic patients that also suffer from AIA usually know it, because small portions of wine or beer trigger the condition. It is partially associated to race: asthmatic Caucasians have a prevalence of 33% [19], while Asian asthmatic patients have a higher prevalence (55%) and more severe AIA [20]. Therefore, asthmatic and AIA patients must be excluded from ethanol-inhaled treatment.

The mechanisms of AIA are not fully understood, but it is not known to be a typical asthmatic reaction [19]. Responders display significantly higher serum levels of acetaldehyde and histamine [19]. Acetaldehyde is the primary metabolite of alcohol, which has a histamine-releasing effect on airway mast cells, thereby increasing the immune response of Th-2 cells and inducing an eosinophilic reaction with increased secretion of IgE and cytokines [19 There are two known mechanisms of serum acetaldehyde increase: in Caucasians it is a fast metabolism in converting ethanol into acetaldehyde by the variant allele of the alcohol dehydrogenase (ADH) 1b variant (rs1229984).19 Meanwhile, Asian patients show a slow degradation of acetaldehyde by a genetically decreased activity of acetaldehyde dehydrogenase 2 (AIDH2) [20].

Regarding possible neurological effect of inhaled ethanol, there are no known reports of serious adverse effects in the literature. Not even a lathe machinist with neurological alterations secondary to a daily exposition during three years to several hours of 100% ethanol at work, which was resolved ad integrum after one month of ethanol withdrawal [21]. Also, blood levels of inhaled ethanol are pretty low: application of 96% alcohol inhaled for 30 minutes, reach a serum level of 0.01%, 15 far from the 0.08% for the legal definition of drunkenness in the USA. All these data strongly suggest that the low dose of 20% for 10 minutes for our patients, would pose any risk of systemic damage.

2.3. Objective

The present study makes a retrospective analysis of three patients with severe COVID-19 treated with 20% ethanol nebulizations, as a co-adjuvant treatment, in addition to the usual medical anti-COVID care of that time, azithromycin or oseltamivir plus ibuprofen. The patients developed the disease during the second wave of the pandemic. Treated patients were compared against five control patients with quite similar clinical characteristics and general anti-COVID treatment, but no inhaled ethanol. Our study also reviews the historical use of this therapy for respiratory diseases since the 1950s, including a search and survey of MDs with experience applying this treatment to respiratory diseases. The present work confirmed the broad precedents of its use, a very low toxicity, as well as the efficacy against severe COVID-19.

3. Material and Methods

The present case report is a retrospective, observational, and controlled study of three patients with severe COVID-19, who received a co-adjuvant therapy of 20% nebulized ethanol, for 10 minutes, three times a day. Patients received also the standard anti-COVID-19 therapy with only ibuprofen, or ibuprofen plus

azithromycin or oseltamivir, as used to be treated the disease on that time, December 2020, during the second wave of the pandemic. Treated patients were compared against five contemporary controls with severe COVID-19, with very similar clinical characteristics, and treatment, but no ethanol therapy. All patients lived in Mexico City (at an altitude of 2200 meters) and contracted the disease in December 2020. Patients were followed-up by telemedicine for clinical evaluation and treatment. The patients were also analyzed one month and one year after the acute clinical picture.

The main short-term outcomes analyzed were the change in dyspnea and blood O2 levels after the ethyl inhalation session and the duration of the acute disease. For the long-lasting sequelae, we evaluated ten symptoms one month and one year after the initial illness: asthenia, arthralgia, headache, dyspnea, anosmia, mental confusion, anxiety, palpitations, chest pain, and cough.

3.1. Treatment Scheme for Inhaled Alcohol

Based on the previous applications summarized in Table 1, we prescribed inhalation therapy of 20% ethanol, three times daily, for 10 minutes per session. The patients prepared a homemade ethanol solution by mixing one cup of 70% ethylic alcohol with three cups of drinkable water to reach the required therapeutic dose. The solution was administered using an ordinary cool-mist humidifier, as shown in Figure 1.

Classification of COVID-19 was based on the World Health Organization criteria. Treated and control patients are classified as having severe COVID-19 when they exhibited a SpO2 > 90%; signs of pneumonia, anosmia, and ageusia; as well as a grade III dyspnea based on the New York Heart Association functional classification, which includes a marked limitation in activity due to dyspnea during less-than-ordinary exercise (e.g., walking short distances 20–100 meters) and comfort only at rest.

Table 1: Summary of previous applications of ethanol therapy. Based on antecedents 2–4 of this table, we decided to use a dose of 20% ethanol for 10 minutes, three times daily.

	Use	[Et-OH]	Time of application	Observations	Reference
1	Clinical phase II trial	65%	45 min	High dose	Castro-Balado 2023.[9]
2	Healthy human volunteers. Comparison of different doses	10%, 15%, and 25%	10 min	Ethanol 15% has a good anti-foaming effect and low irritation.	Quiajiao 2012.[11]
3	Pulmonary edema and croup	20%	10 min	Good therapeutic effect	Maza-Toledo 1998,[i] and Table 3.
4	Croup or difficult-to-control cough	20%	10 min	Three times per day	Survey (Table 3)
5	Pulmonary edema	96%	30 min	High ethanol concentration	Luisada 1952.[15]

Abbreviations: Et-OH: Concentration of ethanol.

Figure 1: Humidifier used by our patients for ethanol therapy. We must clarify that the interviewed MDs used mainly micro-nebulizer as method for administering the ethanol at hospital.

3.2. Review of the Inhalator Ethanol Therapy

The present work complements information with a small bibliographical review and a survey. For this review we used the words “inhaled ethanol therapy”, or “acute pulmonary edema, AND inhaled ethanol therapy”. Both searches were made since 1950. The review was made on June 2023.

For the survey, first we searched among five medical associations, and found six physicians who had applied ethanol therapy for respiratory diseases. In addition to gathering their personal data, the main questions in the interview were about: i) the approximate time, in years or months, in which the MD applied this therapy. ii) The kind of hospital where they applied it (first, second, or third level; public or private). iii) The service where they applied this co-adjuvant therapy. iv) The disease in that they applied it. v) The approximate number of treated patients; and vi) the observed beneficial or adverse effects. The hospitals where the ethanol therapies were applied had authorization from each hospital’s clinical ethics committee or their respective hospital authorities.

3.3. Ethical Statement

Several reasons justified the compassionate use of the ethanol the-

rapy to our patients. First, the compassionate per se, defined as the use of a different application for a known drug not yet approved by health authorities to treat a severe disease when it has no available effective treatment, which was the case of SARS-Cov-2 in December of 2020. Second, the broad use of ethanol therapy here documented with the bibliography and the survey; both investigations corroborated the minimal risk and high possible benefit of ethanol therapy. Third, in that time, our proposed clinical trial to evaluate the antiviral effect of inhaled alcohol in patients with COVID-19 had the first approval by the Comité Hospitalario de Investigación of the COVID Hospital of Querétaro. Also on that time, some COVID-19 patients who learned about our inhaled ethanol therapy requested that we provide them this treatment; the patients were seriously sick and had no precedents for asthma or AIA. Our patients gave us oral and written informed consent. Finally, our study complies with the Helsinki Declaration on studies involving human subjects.

4. Results

4.1. Clinical Picture of the Patients

The three treated and five control patients had severe COVID-19, with signs of severe acute respiratory syndrome (SARS), with a constant low peripheral oxygenation level between 82% and 88%, as measured by pulse oximetry while breathing ambient air (Table 2). The patients had no record of asthma or other dangerous COVID-19 comorbidities, such as immunosuppression, obesity, diabetes, or hypertension. Their standard COVID-19 treatment for the control and observational patients was azithromycin or oseltamivir as an anti-covid drug, plus ibuprofen, or only paracetamol, and intermittent supplemental oxygen therapy. Currently, we know that neither azithromycin nor oseltamivir has an anti-COVID-19 effect, but it was the prevailing regular treatment at the time. All eight patients developed the disease during the second pandemic wave, caused by the B.1.1.519 Delta strain of Coronavirus; characterized by three amino acid changes in the spike protein: T478K, P681H, and T732A. Importantly, this strain increases of 1.85 over non-B.1.1.519 patients for developing a severe/critical outcome.

Table 2: Main clinical data and outcomes of COVID-19 patients
Dyspnea: (++) Mild (+++) Severe (++++) Extreme
Anosmia: (-) Not anosmia (+ -) Hyposmia (+) Anosmia
Ageusia: (-) Not ageusia (+ -) Hypogeusia (+) Ageusia
Chest X-ray, summary:
(a) Symmetric opacity in both basal regions.
(b) Basal opacity in only one of the lungs.
(c) Increased bronco-vascular opacity.
(d) Discrete cardiomegaly.
The list of the analyzed sequels can be seen in the caption in Fig. 3.

	Treated patients			Control patients				
Patient no.	**1**	**2**	**3**	**1**	**2**	**3**	**4**	**5 ***
Age and sex	56 F	60 M	65 M	57 F	70M F	52 F	71 F	40 F
Dyspnea	+++	+++	+++	+++	++++	++	++	-
Anosmia	+	+	+	+	+ -	+	+ -	-
Ageusia	+	+	+	+	+ -	-	-	-
Et-OH therapy	Yes	Yes	Yes	No	No	No	No	No
SpO_2 basal level	86	88	87	82	88	84	86	84
SpO_2 after ethanol therapy	90	94	92	-	-	-	-	
Chest X-ray	b, c, d	a, d	ND	b, d	a, d	a, c	ND	ND
Recovery time (days)	22	20	21	19	35	65	26	46
PCR	+	+	+	+	ND **	Ag+	ND **	Ag+
Sequelae: one month	8	4	5	17	17	9	3	6
Sequelae: one year	3	0	0	2	9	NA	3	NA

Abbreviations: Et-OH: ethanol. F: Female. M: Male. NA: Not available. ND: Not done. Ag+: Molecular diagnosis by antigen test.
(*) This patient had a low saturation of O2 (84%) but with silent hypoxemia.
(**) These patients had no PCR test, but their COVID-19 diagnosis was based on clinical features and epidemiological associations.

4.2. Outcomes

The ethanol co-adjuvant treatment caused an immediate decrease in dyspnea severity and an average increase of SpO2 by 5%, after each therapy session, reaching a SpO2 near or over 90%; it shortened the duration of acute disease, averaging 21 days, against 31.5 days in control patients (Figure 2). Two patients by their own initiative, took an extra dose of ethanol before sleeping and reported an important sleeping improvement; it was corroborated by a third patient, who was not included in the present work because it was a milder case of COVID-19 (SpO2 > 92%).

In the long term, treated patients also had fewer sequelae (Figure 3): One month after the disease, non-treated patients had most of the ten enlisted symptoms and several of them in a severe level. Especially worrying sequels in two control patients were the presence of severe or moderated, but long lasted headache, mental confusion, anosmia, and dyspnea. Meanwhile, ethanol-treated patients had much less and in mild level of sequels (Figure 3).

4.3. Bibliographic Review and Survey

The present paper makes a small bibliographical review of ethanol therapy, that is presented as the introduction section of the article, and summarizes the experience in the use of this therapy for pulmonary edema during more than 70 years.

The MDs' survey found that there has been a systematic application of the ethanol therapy in third-level Mexican hospitals, since the 1970s until recent times (Table 3). The physicians interviewed confirm that alcohol therapy causes an immediate improvement in breathing, characterized by decreased wheezes, coughs, and respiratory obstruction. None of the MDs observed collateral secondary effects nor increased inflammation or symptoms in patients with viral respiratory infections under ethanol inhalation. The application of inhaled-ethanol for croup patients was an important precedent for COVID-19 because laryngotracheitis is caused mainly by viruses. Finally, the two recent reports of phase II protocols,11,12 with the present case-report consolidate a broad experience of this treatment, and is one more evidence of the useful and safety of inhaled ethanol therapy in this context.

Table 3: Summary of the survey of physicians with experience in inhaled alcohol treatment. None of the physicians remembered seeing patients with adverse effects. It is highly valuable that most applications were in public second and third-level hospitals.

MD	Service	Kind of hospital	Use	Approx. time of use	[Et-OH]	Approx. No. of patients	Adverse effects observed?
1	Pediatrics	Public 3rd level	Croup and pulmonary edema	20 years (1985–2005)	20%	600	No
2	Pediatrics and adults	Public 2nd level and private office.	Croup	10 years (2010-2020)	13%	230	No
3	Pediatrics	Public 3rd level	Croup	One year (1985)	20%	40	No
4	Pediatrics	Public 1st level	Croup	Two months (2004)	20%	15	No
5	Adults ICU	Public 3rd level (oncology hospital)	Difficult-to-control cough	Two years (2013–2015)	20%	160	No
6	Adults Emergency room	Public 3rd level	Pulmonary edema	15 years (1970–1985)	10%	1,500	No

Abbreviations: [Et-OH]: Ethanol concentration. ICU: Intensive care unit. MD: Medical doctor. No: number.

Extra data, as specified by the interviewed physicians.

- MD 1 and 2. These MDs added salbutamol to ethanol, as a bronchodilator in pediatric patients older than four years old.
- MDs 3 and 4. They only observed the application of inhaled ethanol by an attending physician during their medical residency. Therefore, they have a limited experience.
- MD 5. In this ICU they prefer inhaled alcohol instead of acetylcysteine for difficult-to-control cough, because the latter causes high respiratory dryness.
- MD 6. This Physician applied inhaled ethanol to a large population of patients, from 1975 to 1985, and never saw secondary effects.

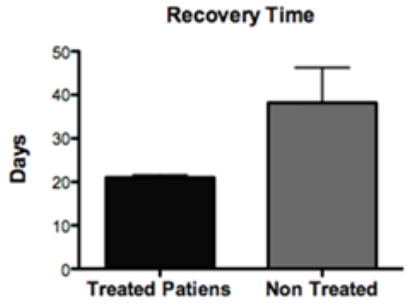

Figure 2: Shorter length of disease in COVID-19 patients treated with ethanol. Comparison of days with acute disease between the patients treated (N = 3) and non-treated (N = 5).

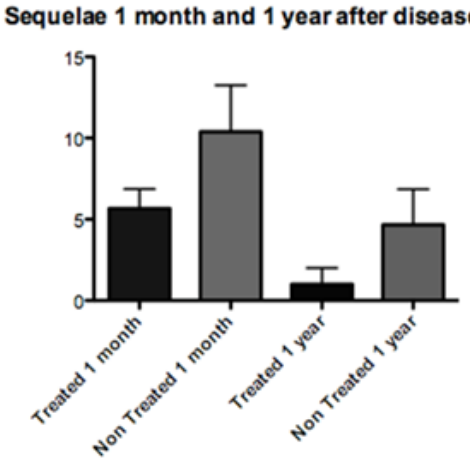

Figure 3: Decreased COVID sequelae in ethanol-treated patients. Analysis one month and one year after the disease showed a decrease in sequelae in treated patients. We asked about ten symptoms, listed in the Material and Methods section. A value of 1 for mild, 2 for moderate and 3 for severe symptoms was assigned. The average for the three patients with co-adjuvant treatment and the five control patients is presented.

5. Discussion

Inhaled ethanol therapy was associated with good clinical outcomes in the three patients with severe SARS-CoV-2 treated with ethanol: decreased dyspnea, increased SpO2, enhanced sleep quality, and prevented several mid and long-term sequelae (Figures 2 and 3). The five control patients helped to validate the ethanol inhalation protocol: with similar characteristics of severe COVID-19, high risk, and in the same epidemic wave. It is important to stress the good outcome of the patients, nonetheless they suffered a severe clinical picture of COVID-19, characterized by an infection with a virulent strain of Coronavirus,26 the low level of SpO2, and their age over 50 years old of the treated patients.

5.1. Wide Experience in Ethanol Inhaled Treatment

The bibliographic review complemented by the survey, showed that inhaled ethanol has been used for more than 70 years, with low toxicity and for several respiratory diseases. It also shows that possible cases of AIA secondary to inhaled alcohol are mild bronchoconstriction and can be treated relatively easily and successfully with only salbutamol. Nevertheless, it is important to exclude asthmatic or AIA patients from this therapy.

The survey to MDs showed that inhaled ethanol therapy has been systematically applied for croup in Mexican third level hospital, even though there are no previous scientific reports of this application. The survey also confirmed the efficacy of this therapy with an immediate improvement, no serious adverse effects, neither an increase in symptoms nor inflammation in patients with a viral respiratory infection.

5.2. Possible Mechanism of Action of Ethanol in COVID-19

Ethanol has several effects at local level: The immediate decrease in dyspnea and increase in SpO_2, are secondary to the well-known anti-foaming and expectorant effect, well described for pulmonary edema [11]. The other beneficial effect must be secondary to the direct viricidal effect: dissolving of lipidic membrane by ethanol is well documented [7]. We hypothesize that the viricidal effect of alcohol in the respiratory tract could be the cause of a decreased viremia and lead to the short and long term good outcomes in our patients (Figure 3).

In human research, report of cases and proof of concepts are highly valuable [29], they help in the decision to proceed or not to large protocol, with significant health and economic implications for patients, hospitals, and researchers [30]. Our results, together with the contradictory results between the Santiago de Compostela University and Mansoura University, confirm the need of a comprehensive, prospective, and controlled phase II protocol.

The present study is essentially a case report, and because of its retrospective nature it may have some bias and gaps in the research, mainly a lack of detailed clinical and diagnostic laboratory information. Because of that, the present research is still not conclusive until a full phase II protocol is made, which we are proposing in the COVID Hospital of Querétaro State, Mexico, to evaluate this treatment in a statistically significant sample of patients.

5.3. Comparison of Our Results with Other Ethanol Inhaled Treatments

In summary during the present pandemic, there have been five reports on the use of on inhaled ethanol therapy against COVID-19: two theoretical, and three with clinical experimental protocols, two of them significantly enhanced the outcomes of the patients.

The Egyptian protocol with inhaled 35% ethanol, reported modest but statistically significant good outcomes [9]; although they administered only three inhaled puffs of spray every six hours. Our treatment scheme, with inhalation sessions for 10 minutes, consisted of many more respiratory cycles, three times a day, which led to a much deeper impregnation of alcohol on the respiratory tract. The Spaniard protocol with a 65% ethanol and oxygen, did not reveal any differences between treated and control patients;

however, they applied the co-adjuvant treatment only in patients with a SpO_2 over 93%. Our protocol on the contrary, applied the therapy in patients with a much lower SpO_2, between 82% and 88%, that immediately enhances dyspnea, increasing the SpO_2 level. The expectorant-antifoaming effect seems to be essential to our contrasting good outcome.

6. Conclusions

The inhaled ethanol therapy here applied reduced the intensity of the disease and sequelae, providing new evidence of its sound, practical and easy-to-apply, even in ambulatory patients of the present treatment. The bibliographical review and the survey corroborate its safety, with a vast experience and positive outcomes.

The present report provides valuable additional information to the two recent clinical phase II protocols,: i) it reviews the broad experience of inhaled ethanol treatment for pulmonary edema and croup; ii) it analyzes the possible activation of mild AIA, concluding that does not represent a big deal, because it is not a severe syndrome, and it can be avoided by excluding patients with asthma or AIA precedents; iii) our report tips the scale toward the good outcomes for this treatment.

The present report is one more evidence that ethanol-inhaled therapy can be a new and affordable treatment against SARS-CoV-2, especially in low-income countries. Also, as most viruses are susceptible to ethanol, this treatment can be tried with other viral respiratory diseases, such as influenza or respiratory syncytial virus.

Finally, the combination of theoretical and practical results reported here yields excellent information about this treatment, resolves some primary challenges, and provides new evidence of its low risk, ease of application, and reasonable outcomes.

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