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Effects and safety of hypertonic saline combined with airway clearance in non-hospitalized children with recurrent wheezing

Vanesa González-Bellido[1], Verónica Veláz-Baza[1], Noelia Rama-Suárez[1], Carmen Jimeno-Esteo[2], Josep Sirvent-Gomez[3], Juan Nicolás Cuenca-Zaldívar[4,5,6,*], Sari Mayorales-lises[7], Márcio Vinícius Fagundes-Donadio[8,9] and Samuel Fernández-Carnero[4]

[1]*Fisiobronquial Physiotherapy Clinic, Madrid, Spain*

[2]*Fisiobronquial Physiotherapy Clinic, A Coruña, Spain*

[3]*Hospital Materno Infantil Teresa Herrera, A Coruña, Spain*

[4]*Universidad de Alcalá, Facultad de Medicina y Ciencias de la Salud Departamento de Enfermería y Fisioterapia, Grupo de Investigación en Fisioterapia y Dolor, 28801 Alcalá de Henares, Spain*

[5]*Research Group in Nursing and Health Care Puerta de Hierro Health Research Institute — Segovia de Arana (IDIPHISA), Madrid, Spain*

[6]*Primary Health Center "El Abajón", Las Rozas de Madrid, Madrid, Spain*

[7]*Managing Director Hospital Quirónsalud San José, Madrid, Spain*

[8]*Laboratory of Pediatric Physical Activity, Centro Infant Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, Brazil*

[9]*Departmento de Fisioterapia, Facultad de Medicina y Ciencias de la Salud Universitat Internacional de Catalunya (UIC), Barcelona, Spain*

*nicolas.cuenca@salud.madrid.org

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*Corresponding author.

Background: The International Study of Wheezing in Infants defines recurrent wheezing as the presence of three or more medically documented episodes of wheezing within one year. To date, there is no evidence on the use of hypertonic saline (HS) combined with airway clearance techniques (ACT) for children with recurrent wheezing treated in an outpatient setting. Therefore, this is the first study to explore the use of such interventions in infants with recurrent wheezing.
Objectives: To evaluate the effects and safety of a three-month protocol including HS and ACT for non-hospitalized infants with recurrent wheezing.
Methods: Randomized, double-blind, controlled trial, including outpatient infants with recurrent wheezing. Children were randomized to either 3% HS or 0.9% saline groups and were treated with bronchodilator and nebulized with the respective solutions before ACT. The primary outcome was the Wang score. Secondary outcomes included the number of hospitalizations and respiratory crisis, need for rescue medication, and school absences. All variables were measured during the three previous months from inclusion and during intervention period. The study protocol was registered at ClinicalTrials.gov (NCT04331496) on March, 31, 2020.
Results: Forty children were included. Regarding immediate effects, significant differences ($p < 0.001$) were found for time, but not for group or interaction (group × time), in all outcome variables (increase in SpO_2, decrease in heart and respiratory rate, wheezing episodes, retraction, and Wang score). Comparing the previous three months with the study period, there were significant differences in both groups for the severity of crisis ($p < 0.001$) and medication steps ($p = 0.002$).
Conclusion: A three-month protocol including HS and ACT for outpatient infants with recurrent wheezing was safe and reduced morbidity. No differences were found between the use of HS and 0.9% saline.

Keywords: Recurrent wheezing; prolonged slow expiration; hypertonic saline; airway clearance.

Introduction

The International Study of Wheezing in Infants defines recurrent wheezing as the presence of three or more medically documented episodes of wheezing within one year.[1] Episodes usually result from airflow disturbance due to reduced calibre of the lower airways caused by obstruction or constriction.[2] Recurrent wheezing in children may be associated with viral respiratory infections and asthma, as well as other pulmonary or extra-pulmonary diseases.[3] It is highly prevalent in the first two to three years of life, reaching 12.4% of children in European countries and up to 19.3% in Latin America,[4] causing severe morbidity, affecting the quality of life and generating significant costs for national health services.[3] Studies have analysed several aspects related to recurrent wheezing, such as the high frequency of emergency department visits, hospitalizations and the use of different treatments, with varying scientific evidence, including inhaled bronchodilators, inhaled corticosteroids, oral corticosteroids, leukotriene receptor antagonists, antibiotics, paracetamol, and others.[2] However, there is still high variability in clinical practice regarding the use of additional treatments, including airway clearance techniques (ACT), and hypertonic saline (HS) inhalation. Although there is considerable evidence for the use of ACT in infants admitted for acute viral bronchiolitis (AVB),[5] very little is known about its use in outpatient settings for infants diagnosed with recurrent wheezing. The use of ACT aims to reduce airway obstruction, improve gas exchange, and reduce respiratory burden.[6] This may contribute to preventing flare-ups and future complications, as it is estimated that more than half of adults with asthma were already asthmatics in childhood.[7] Indeed, there is also evidence that the association of ACT with HS inhalation can lead to acute benefits,[8] although the use of HS alone remains controversial, as there are studies showing no benefits for infants with AVB.[9]

To date, there is no evidence on the use of HS combined with ACT for children with recurrent wheezing treated in an outpatient setting, only studies in non-hospitalized infants with AVB, highlighting its safety for this population.[10] Therefore, this is the first study to explore the use of such interventions in infants with recurrent wheezing. The objective here was to assess the main clinical effects and safety of a three-month protocol including HS and ACT for infants diagnosed with recurrent wheezing and referred to an outpatient setting for follow-up. The effects of adding HS (3%) were studied by comparing to a

0.9% saline group. In addition, retrospective data from the three previous months from inclusion were collected as a control for morbidity data. We hypothesized that the use of HS combined with ACT would contribute to reducing morbidity during the three months of intervention compared to the previous three months.

Methods

Design

A randomized controlled clinical trial with two parallel groups following the Consolidated Standards of Reporting Trials guidelines.[11] A repeated measures design was used, with retrospective data from the three months prior to inclusion serving as a control. The study was approved by the Research Ethics Committee of the Hospital Príncipe de Asturias (EC 08/2019) and all parents or legal guardians signed an informed consent form prior to inclusion. All procedures were conducted in accordance with the amended Declaration of Helsinki. The study protocol was registered at ClinicalTrials.gov (NCT04331496).

Participants

A convenience sample of 49 children was recruited between November 2020 and January 2021. Patients had to meet the following inclusion criteria: (i) Age between six and 36 months; (ii) Follow-up in the pediatric pulmonology service with at least one previous visit to the clinic before the start of the study; (iii) Medical diagnosis of recurrent wheezing; (iv) No previous ACT since diagnosis; (v) Legal guardian's consent to participate by signing the informed consent form. The following exclusion criteria were adopted: (i) Comorbidities such as cardiac, neurological or traumatic diseases, congenital anomalies, chronic lung disease such as bronchodysplasia; (ii) Severe obstruction with a score > 8 according to the Wang score.[12]

Randomization

Children were randomized into two groups: 3% HS and 0.9% saline. An independent investigator assigned participants to each group in a concealed manner using sealed opaque envelopes. In each envelope, the allocation number to either group was included; these numbers were generated by simple random sequences using R software version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). Parents and/or legal guardians were blinded to the treatment groups.

Airway clearance techniques in children with recurrent wheezings

Both experimental groups underwent the same treatment protocol, as described below, except for the use of hypertonic (3%) or standard (0.9%) saline. The bronchodilator (salbutamol), as prescribed by the pediatric physician, was administered to the children via the holding chamber (2 puffs) 20 min prior to the use of ACT. After 10 min, 4 mL of 3% HS or 0.9% saline was nebulized using a vibrating mesh nebulizer (Phillips Respironics, Pennsylvania, USA). Experienced and trained physiotherapists performed all ACT techniques. The ACT protocol consisted of a standard 20 min session comprising of sitting nasal irrigation, prolonged slow expiration (PSE), and induced cough. PSE is a passive expiratory support technique applied to infants using slow thoracoabdominal pressure, starting at the end of spontaneous inspiration and continuing through the reserve expiratory volume. After the application of PSE, coughing was triggered by applying thumb pressure just above the sternum at the end of the inspiratory phase. The physiotherapist then used a finger inserted from the corner of the mouth to draw mucus from the inside of the mouth, towards the outer edge. Treatment sessions were performed every three weeks for a total period of three months. The pharmacological treatment was recorded considering the therapeutic steps described by the "Spanish Guidelines for the management of asthma".[7]

Study outcomes

The primary outcome of the study was the assessment of the Wang clinical severity score. Secondary outcomes included the number of hospitalizations for respiratory reasons, the need for rescue medication, the number of respiratory crises and absences from infant school, which were evaluated during the intervention period and assessed retrospectively for the three months prior to inclusion.

Clinical status evaluation

Parents or legal guardians from infants who met the inclusion criteria were asked to complete a

questionnaire with information regarding the participant's clinical status in the three months prior to the inclusion in the study. The questionnaire contained information on the number of hospitalizations for respiratory reasons, the need for use of rescue medication, the number of respiratory crises, and absences from infant school. These variables were also prospectively monitored during the three months of the study protocol by weekly telephone contact.

Afterwards, a pediatric physician experienced in the evaluation of infants with recurrent wheezing and blinded to the study groups classified the infants according to the clinical severity score proposed by Wang,[12] as well as measured respiratory rate, peripheral oxygen saturation (SpO_2), and heart rate (HR) using a pulse oximeter (Massimo®, Irvine, California, USA). These measurements were performed at baseline (T0), 10 min (T10) after inhalation and 40 min (T40) after ACT. This clinical evaluation was performed at all treatment sessions.

Wang clinical severity score

The Wang scale[12] is a quantitative scale designed to assess clinical severity in patients with acute viral bronchiolitis. It assigns a value between 0 and 3 to each of four variables: Respiratory rate, wheezing, chest retraction, and general condition. The overall score is graded as mild (1–3), moderate (4–8) or severe (> 8), with the maximum score being 12 and the minimum 0, which indicates normality. Therefore, a higher score indicates a worse condition. The different variables used in the Wang score have a good level of agreement between physicians, nurses, and physiotherapists (kappa = 0.72 [95% CI: 0.66–0.78]).[12–14]

Safety and adverse effects

Adverse events were monitored and recorded throughout the treatment period and up to 40 min after the end of treatment. The main adverse events monitored were bronchial constriction (bradycardia and desaturation), chest retraction, wheezing, epistaxis, coloured skin, vomiting, and tachycardia. If parents or legal guardians requested the physiotherapist to stop treatment, the information and the reason for the request were also recorded.

Sample size

Considering the absence of similar studies in children with recurrent wheezing, the final Wang score of the first 20 children who finished protocol (10 children per group) was used to estimate the required sample size. This approach is commonly used in pilot studies with the aim of calculating the sample size for the main study.[15–17] Estimation with a mixed ANOVA indicated that 40 children (20 per group) were needed, accepting a risk of type 1 error of 0.05 and a power of 90%.

Statistical analysis

Statistical analysis was performed using R 3.5.1. The significance level was set at $p < 0.05$. The Shapiro–Wilk test was used to determine the non-normal distribution of quantitative variables. Qualitative variables are described as absolute values and relative frequencies, and quantitative variables are described as median and interquartile range or mean and standard deviation. Outcome variables were analysed using a robust mixed analysis of variance ANOVA-Type Statistic (ATS) with one within-subjects factor (repeated measures) and one between-subjects factor (both groups) and the effect size was defined with partial η^2 as 0.01–0.06 (small), 0.06–0.14 (moderate), and > 0.14 (large).[18] The Wilcoxon signed-rank test between repeated measures, with Bonferroni correction, was applied as a post hoc test. For the number of kindergarten absences, number of crisis and hospitalizations, the Mann–Whitney U-test between groups, or the Wilcoxon Signed Rank test between repeated measures was applied. Qualitative variables were analysed using Fisher's exact test.

Results

In total, 921 children were screened, and 872 were excluded. The reasons for exclusion and the flow chart of the study are presented in Fig. 1. The final sample consisted of 40 children randomized to the hypertonic solution group ($n = 21$) and the saline group ($n = 19$). The baseline characteristics of the subjects are shown in Table 1. The mean age of the infants was 15.35 ± 5.27 months. No significant baseline differences were found between the two groups.

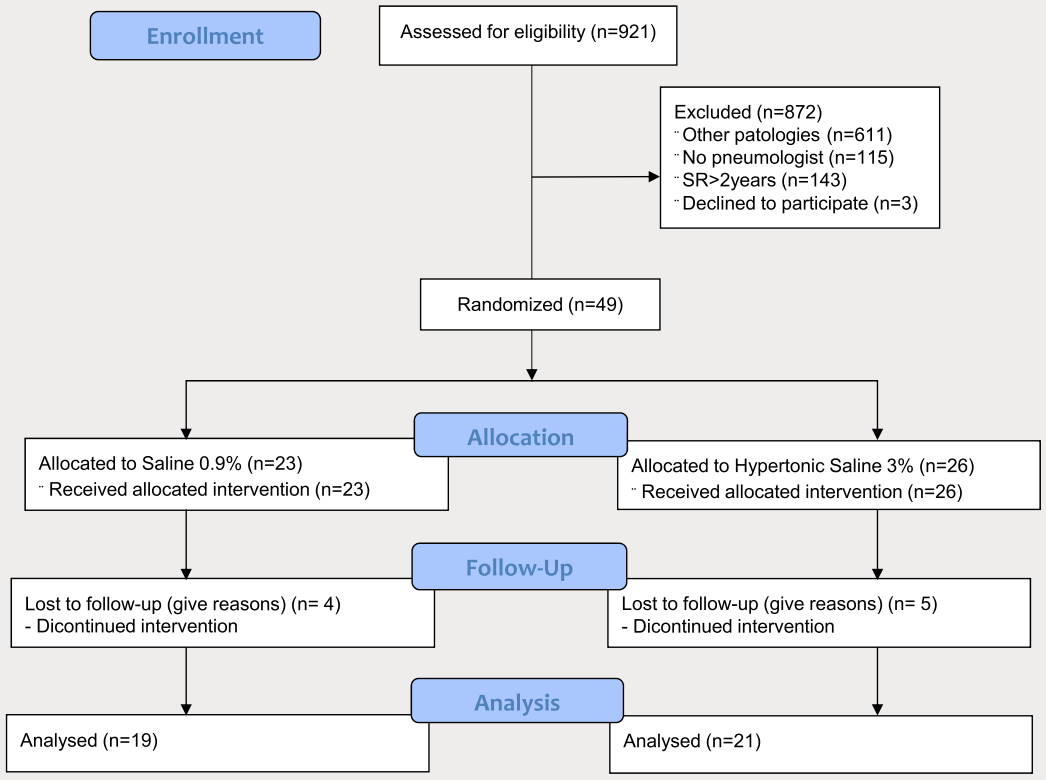

Fig. 1. Flow chart of the study.

Table 1. Baseline characteristics of participants.

	Hypertonic saline 3% ($n = 21$)	0.9% saline solution ($n = 19$)	[a]p-value
Age, months	15.35 ± 5.27	16.36 ± 6.40	0.559
Clinical diagnosis, n (%)			
Recurrent wheezing	21 (100.0)	19 (100.0)	> 0.99
Siblings, n (%)			
No	7 (33.3)	6 (31.6)	> 0.99
Yes, in kindergarten	14 (66.7)	13 (68.4)	
Household tobacco use, n (%)			
No	19 (90.5)	17 (89.5)	> 0.99
Yes	2 (9.5)	2 (10.5)	
Attending kindergarten, n (%)			
No	4 (19.0)	3 (15.8)	> 0.99
Yes	17 (81.0)	16 (84.2)	
Associated diseases, n (%)			
None	6 (28.6)	8 (42.1)	0.358
Allergy	9 (42.9)	4 (21.1)	
GER	1 (4.8)	3 (15.8)	
GER and allergy	5 (23.8)	4 (21.1)	

Note: GER: gastro-esophageal reflux. Data expressed as mean ± standard deviation or absolute and relative values (%). [a]significance level set at $p < 0.05$.

For immediate effects, the mixed robust ANOVA test showed significant differences for measurement time (main effect for time) in each group, for all outcome variables: Wang score ($F(1.616, 0) = 401.737$, $p < 0.001$) (Fig. 2(a)); SpO_2 ($F(1.357, 0) = 145.658, p < 0.001$) (Fig. 2(b)); HR ($F(1.379, 0) = 59.525$, $p < 0.001$) (Fig. 2(c)), respiratory rate ($F(1.516, 0) = 396.376, p < 0.001$)

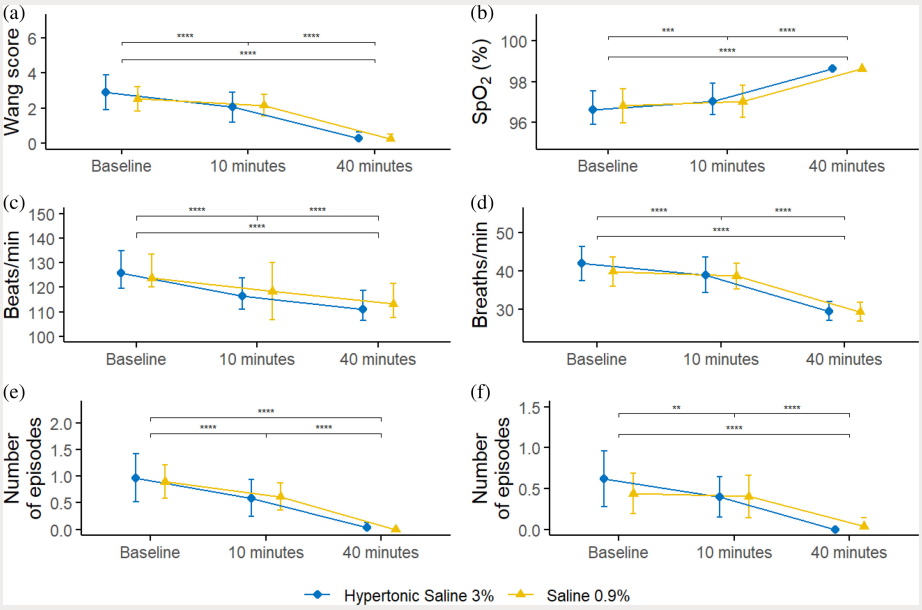

Fig. 2. Immediate effects of using 3% hypertonic saline or 0.9% saline on (a) peripheral oxygen saturation, (b) heart rate, (c) respiratory rate, (d) Wang score, (e) number of wheezing episodes, and (f) number of chest retraction episodes. ****indicates significant differences at $p < 0.0001$, ***indicates significant differences at $p < 0.001$ and **indicates significant differences at pΓ0.01 (Wilcoxon signed rank test).

(Fig. 2(d)), number of wheezing episodes ($F(1.819, 0) = 148.328$, $p < 0.001$) (Fig. 2(e)) and retraction ($F(1.627, 0) = 80.438$, $p < 0.001$) (Fig. 2(f)) with small and significant effect size in all of them (Supplementary material Table S1).

There were no significant differences between the two groups (main effect for group) in the Wang score ($F(1, 228.512) = 0.268$, $p = 0.605$), SpO_2 ($F(1, 150.024) = 0.128$, $p = 0.721$), HR ($F(1, 261.654) = 0.048$, $p = 0.827$), respiratory rate ($F(1, 1) = 0.692$, $p = 0.406$), number of wheezing ($F(1, 133.023) = 0.161$, $p = 0.689$), and retraction ($F(1, 140.785) = 0.723$, $p = 0.397$). In addition, there were no significant differences in all outcome variables for the interaction (groups × measurement time): Wang score ($F(1.616, < 0.001) = 3.624$, $p = 0.36$), SpO_2 ($F(1.357, < 0.001) = 0.521$, $p = 0.524$), HR ($F(1.379, < 0.001) = 1.964$, $p = 0.155$), respiratory rate ($F(1.516, < 0.001) = 3.1$, $p = 0.059$), number of wheezing ($F(1.819, < 0.001) = 0.437$, $p = 0.627$) and retraction ($F(1.627, < 0.001) = 3.899$, $p = 0.28$).

Post hoc tests showed significant differences between all measurements over time, revealing an increase in SpO_2 values and a decrease in heart and respiratory rates, number of wheezing episodes, retraction and Wang score in both groups. In terms of adverse events, 90.5% of children in both groups had no adverse events during the entire treatment period; and in those who did (9.5%) there were only mild effects in the form of coloured skin or epistaxis.

Data that were compared three months before the study and three months during the study were analysed (Table 2). Fisher's exact test showed significant differences in the hypertonic and saline groups for seizure severity ($p < 0.001$ for both) and medication steps ($p = 0.002$ and $p = 0.005$, respectively). In both groups, the number of seizure-free children increased and the number of moderate or severe seizures decreased, as well as there were fewer children in a 2A medication step and more in a 2B step. No significant differences were observed for the use of rescue medication. The Wilcoxon Signed Rank Test showed significant differences in the number of absences from kindergarten before and during the study period for both groups ($Z = -3.92$, $p < 0.001$ and $Z = -3.771$, $p < 0.001$, respectively), indicating a significant reduction in the study period (Table 2).

The Wilcoxon Signed Rank test also showed significant differences between times in the number of crisis ($Z = 5.495$, $p < 0.001$) (Fig. 3(a)) and hospitalizations ($Z = 2.902$, $p = 0.003$) (Fig. 3(b)) indicating a decrease during the study.

Table 2. Effects of a 3-month program of airway clearance techniques plus 3% hypertonic saline or 0.9% saline on clinical variables.

	3% hypertonic saline solution ($n = 21$)		0.9% saline solution ($n = 19$)		Group	Group × time
	Before	During	Before	During	[a]p-value	[a]p-value
Severity of crisis, n (%)					0.082	< 0.001
None	8 (12.7)	42 (66.7)	8 (14.0)	38 (66.7)		
Mild	18 (28.6)	19 (30.2)	26 (45.6)	17 (29.8)		
Moderate	28 (44.4)	1 (1.6)	13 (22.8)	1 (1.8)		
Severe	9 (14.3)	1 (1.6)	10 (17.5)	1 (1.8)		
Medication use (steps), n (%)					0.297	< 0.001
2A	9 (42.9)	5 (23.8)	7 (36.8)	6 (31.6)		
2B	8 (38.1)	12 (57.1)	11 (57.9)	12 (63.2)		
4	4 (19.0)	4 (19.0)	1 (5.3)	1 (5.3)		
Number of absences from kindergarten, n (%)	5.02 ± 2.86	0,83 ± 0.92	4.82 ± 3.78	0,77 ± 0.75	0.296	Γ0.001
Use of rescue medication, n (%)					0.328	> 0.99
Less than two	0 (0)	19 (90.5)	0 (0)	14 (73.7)		
More than two	1 (4.8)	2 (9.5)	2 (10.5)	5 (26.3)		
More than three	20 (95.2)	0 (0)	17 (89.5)	0 (0)		

Note: 2A: low dose inhaled glucocorticoid (IGC); 2B: low dose IGC + leukotriene receptor antagonist; 4: medium-high dose IGC + long-acting β2-adrenergic agonist (LABA). [a]Significance level set at $p < 0.05$.

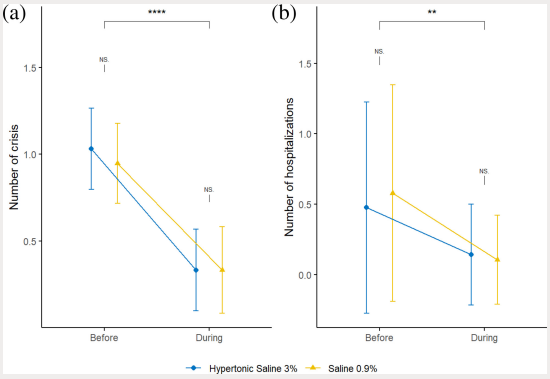

Fig. 3. Effects of a three-month protocol of airway clearance techniques plus 3% hypertonic saline or 0.9% saline on the number of respiratory crises (a) and hospital admissions (b). ns indicates no significant difference (Mann-Whitney U-test); ****indicates significant difference at $p < 0.0001$ and **indicates significant difference at $p < 0.01$ (Wilcoxon signed-rank test).

Discussion

This randomized controlled trial evaluated the effects and safety of the use of nebulized HS prior to ABT in the treatment of infants diagnosed with recurrent wheezing. To our knowledge, this is the first clinical trial conducted in an outpatient setting to evaluate the benefits and safety, over a 3-month period, of HS prior to respiratory physiotherapy. The results have shown that the use of both hypertonic and standard saline was safe and presented similar immediate and positive clinical effects. In addition, when compared to the three months prior to the study, reduced morbidity (number of crisis, hospitalizations and medication use) was found for both groups of infants with recurrent wheezing.

In young children with wheezing, clinical severity is commonly classified according to the frequency and intensity of symptoms.[3] Although no difference was found between 3% hypertonic solution and 0.9% saline, this study has shown that the use of inhalation plus ACT was able to reduce respiratory crisis, medication use, and hospital admissions compared to the period before the start of the study.

Recurrent wheezing has a significant morbidity and it is estimated that about one-third of school-aged children manifest this symptom during the first five years of life. The presence of wheezing in young children, whether transient or persistent, can be severe enough to impact the quality of life, leading to frequent use of the health care system and significant financial costs.[19] Different studies have analysed aspects such as the high frequency of emergency department visits or hospitalizations, leading to a high number of kindergarten absences and parental leave.[2,20] Our data have shown a significant reduction in the number of kindergarten absences during the three-month study period. This can have a positive impact on both

children's development and parents' social/professional activities.

Another important issue in the management of young children with recurrent wheezing in an outpatient setting is the immediate effects and safety of treatment. Our results have shown no differences between groups (0.9% saline versus 3% saline), but significant improvements in SpO_2, HR, respiratory rate, number of wheezing and retraction episodes, and Wang score. This may be relevant acute effects, as exacerbations associated with recurrent wheezing are usually characterized by airway obstruction, inflammation and airway hyperresponsiveness.[21] In the study by Conesa-Segura *et al.*,[5] a single daily intervention accelerated the recovery of children with AVB, reducing the length of stay in intensive care units without the presence of significant side effects.

To our knowledge, this is the first study to present data for the use of ACT in children with recurrent wheezing in an outpatient setting. Recent evidence has shown that the use of ACT was safe for non-hospitalized children with AVB.[10] In addition, in hospitalized children with AVB, few studies have reported the presence of adverse effects, confirming the safety of ACT use.[6] In this study, only mild adverse events (skin discoloration and epistaxis) have been demonstrated.

Our results have also shown that the use of nebulized hypertonic 3% saline prior to ACT produced similar effects compared to 0.9% saline, both immediately and during the three-month intervention period. In addition, no clinically relevant adverse events were found. Although no data on the use of HS for non-hospitalized children with recurrent wheezing were found for comparison, its use for infants with AVB remains controversial in the current literature, as demonstrated by two recent meta-analyses showing both beneficial and no effects from its use.[8,19] Heikkilä and Korppi[9] presented data from studies of infants with AVB showing no beneficial effects for the use of HS, although earlier studies pointed to positive results. On the other hand, the results of the meta-analysis by Chia-Wen *et al.*[22] showed that, compared to the use of physiological saline (regardless of whether children were hospitalized or not), the use of HS improved the severity of respiratory distress, extended sleep time, reduced the frequency of awakening during the night and shortened the length of hospital stay. A lower hospitalization rate was also demonstrated for non-hospitalized children, indicating beneficial effects.[22] Another important aspect is the combination of HS with ACT. Felicio-Junior *et al.*[23] showed that the use of physiotherapy manoeuvres induced sputum with the same quality as the standard technique (HS), without respiratory discomfort or limitations in asthmatic children and adolescents. Therefore, it is possible that the combination of techniques may lead to different results than either of them alone. However, the current data demonstrated that the immediate use of hypertonic and 0.9% saline solutions was safe and, together with ACT, reduced morbidity in infants with recurrent wheezing. The lack of differences between the use of hypertonic (3%) and 0.9% saline may indicate that the combination of inhalation with ACT may be more important than the concentration of the saline solution used. Nonetheless, further studies could still address the use of ACT alone for infants with recurrent wheezing.

We believe it is also important to note that the literature on the field focuses almost entirely on studies involving children with AVB who have been hospitalized.[24–31] Although we have previously demonstrated the clinical effects and safety of the use of high-frequency chest wall oscillation (HFCW)[31] and ACT for non-hospitalized infants with mild to moderate AVB, this appears to be the first study conducted in an outpatient setting with children diagnosed with recurrent wheezing. One of the factors contributing to this scarce literature may be the differential diagnosis between recurrent wheezing and asthma. The GINA[3] and GEMA[7] guidelines, revised in 2022, highlight the difficulty of diagnosing asthma at this age due to the frequency of episodes of upper respiratory infection and the lack of diagnostic tools, such as spirometry, to define bronchial reversibility.

This study also has limitations, including the absence of a control group without inhalation and/or ACT. However, we believe that the evaluation of both interventions together may represent more accurately the clinical use of such techniques, due to their additive effects on mucociliary clearance. In order to minimize that, data from the three months prior to inclusion were used, although the limitations of its retrospective nature may also be recognized. Based on the safety demonstrated here, future studies should confirm the reduction of morbidity found and further explore the effects of each procedure in isolation, longer follow-up periods, and also the best frequency for the use of ACT and inhalation.

Conclusion

The results of this study demonstrated that the use of a three-month protocol combining HS and ACT for infants diagnosed with recurrent wheezing referred to an outpatient setting was safe. Although no differences were found between the use of hypertonic and 0.9% saline, a significant reduction in morbidity was demonstrated. The data presented here may contribute to the clinical management of non-hospitalized young children with recurrent wheezing.

Conflict of Interest

The authors have no conflicts of interest to disclose.

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Author Contribution

Vanesa González-Bellido (VGB) and Samuel Fernández Carnero (SFC) had the main responsibility for the supervision and administration of the project. Verónica Velaz-Baza (VVB), M[a] del Carmen Jimeno Esteo (CJE) and Noelia Rama Suárez (NRS), had the main responsibility of research and writing, reviewing and editing. Vanesa González-Bellido and Samuel Fernández Carnero were mainly responsible for the conceptualisation and methodology. Josep Sirvent Gómez (JSG) and Sari Mayorales Alises (SMA) had the main responsibility for validating the data results and contributed to the writing of the original draft. Juan Nicolás Cuenca Zaldívar (JNC) carried out the formal analysis and data curation, developed the software (analytical code) and wrote the original draft. Vanesa González-Bellido and Verónica Velaz-Baza contributed to the writing — original draft. Márcio Vinícius Fagundes Donadio (MVF) contributed to the conceptualisation, writing — original draft and writing - revision and editing.

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Supplementary Material

Table S1.

	Hypertonic saline 3%			0.9% saline solution						
	Baseline	10 minutes	40 minutes	Baseline	10 minutes	40 minutes	Between groups [a]*p*-value	Within groups [a]*p*-value	Between: within groups interaction [a]*p*-value	Effect size (95%CI)
Wang's score	2.667 [2, 3.667]	1.667 [1.667, 2.667]	0 [0, 0.667]	2.333 [2, 3]	2 [1.667, 2.333]	0.333 [0, 0.333]	0.605	<0.001	0.36	0.01 (0.001, 0.139)
SpO_2 (%)	96.667 [96.333, 97.333]	97 [96.667, 97.667]	98.633 [98.633, 98.633]	96.667 [96.5, 97.333]	97 [96.333, 97.5]	98.633 [98.633, 98.633]	0.721	<0.001	0.524	0.03 (0.001, 0.088)
Heart rate (beats/min)	126.333 [123, 132.667]	118.667 [113.667, 121.667]	111 [107, 118.667]	126.667 [119.833, 130.333]	118.333 [108.833, 126]	116.333 [102.667, 119.333]	0.827	<0.001	0.155	0.021 (0.001, 0.114)
Respiratory rate (breaths/min)	42.333 [38, 46]	39.333 [34.333, 42.667]	29.667 [27.333, 31.333]	40.667 [37.167, 42.167]	39 [35.667, 40.667]	29.667 [27.833, 30.5]	0.406	<0.001	0.059	0.017 (0.002, 0.11)
Number of wheezing episodes	1 [0.667, 1]	0.333 [0.333, 0.667]	0 [0, 0]	1 [0.667, 1]	0.667 [0.333, 0.667]	0 [0, 0]	0.689	<0.001	0.627	0.03 (0, 0.086)
Number of retractions	0.667 [0.333, 0.667]	0.333 [0.333, 0.667]	0 [0, 0]	0.333 [0.333, 0.667]	0.333 [0.333, 0.667]	0 [0, 0]	0.397	<0.001	0. 28	0.009 (0.005, 0.165)

Note: Data expressed with median [interquartile range] and with absolute and relative values (%). 95%CI: 95% confidence interval. [a]Significant level set at $p < 0.05$.