



ORIGINAL

## Safety of aerosol therapy in children during noninvasive ventilation with helmet and total face mask

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### KEYWORDS

Noninvasive ventilation (NIV);  
Drug side effect;  
Bronchial spasm;  
Asthma;  
Bronchiolitis;  
Nebulizers and vaporizers;  
Total face mask;  
Helmet

### Abstract

**Purpose:** To evaluate the consequences of using nebulized drugs in patients subjected to non-invasive ventilation (NIV) with total face mask (TFM) and helmet.

**Design:** A descriptive analytical study of a prospective patient cohort was carried out.

**Ambit:** Pediatric intensive care unit (PICU) of a tertiary hospital.

**Patients:** Consecutive sampling was used to include all patients admitted to the PICU and requiring NIV with helmet or TFM over a period of 29 months. No patients were excluded.

**Interventions:** Nebulized treatment was added according to medical criteria.

**Variables of interest:** Independent variables were age, sex, diagnosis, disease severity, ventilation parameters and nebulized drugs (if administered). Secondary outcomes were duration and failure of NIV, and length of PICU stay.

**Results:** The most frequent diagnoses were bronchiolitis (60.5%) and asthma (23%). Patients received NIV for a median of 43 h. Nebulized drugs were administered in 40% of the cases during NIV, and no adverse effects were registered. Using Bayesian statistics, the calculated probability of suffering an adverse effect was 1.3% with helmet and 0.5% with TFM (high density 95%

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## PALABRAS CLAVE

Ventilación no invasiva (VNI);  
Efectos secundarios;  
Broncoespasmo;  
Asma;  
Bronquiolitis;  
Nebulización;  
Mascarilla facial total;  
Casco

probability intervals). Patients with helmet and nebulized therapy were in more serious condition than those who did not receive nebulization; nevertheless, no differences were observed regarding the need to change to bilevel modality. With TFM, PICU stay was shorter for the same degree of severity ( $p = 0.033$ ), and the NIV failure rate was higher in patients who did not receive inhaled drugs ( $p = 0.024$ ).

**Conclusions:** The probability of suffering an adverse effect related to nebulization is extremely low when using a helmet or TFM. Inhaled therapy with TFM may shorten PICU stay in some patients.

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## Seguridad de la aerosolterapia durante la ventilación mecánica no invasiva con helmet y mascarilla facial total en población pediátrica

### Resumen

**Objetivo:** Evaluar las consecuencias de la medicación nebulizada en pacientes con ventilación no invasiva (VNI) con mascarilla facial total (MFT) y casco.

**Diseño:** Estudio analítico descriptivo sobre una cohorte prospectiva de pacientes.

**Ámbito:** UCIP de hospital de tercer nivel.

**Pacientes:** Todos los pacientes ingresados en UCIP (muestreo consecutivo) con VNI con casco o MFT durante 29 meses. No se excluyeron pacientes.

**Intervenciones:** Se añadió tratamiento nebulizado según criterio médico.

**Variables de interés:** Independientes: edad, sexo, diagnóstico, gravedad, parámetros ventilatorios y medicación nebulizada (si se utilizaba). Secundarias: duración, fallo de VNI y estancia en UCIP.

**Resultados:** Los diagnósticos más frecuentes fueron bronquiolitis (60,5%) y asma (23%). La mediana de conexión a VNI fue de 43 horas. Se administraron nebulizaciones durante la VNI en un 40% sin registrarse efectos adversos. La probabilidad calculada de tener un efecto adverso fue 1,3% con casco y 0,5% con MFT (estadística bayesiana, intervalo de probabilidad 95%). Los pacientes con casco y aerosolterapia tenían mayor gravedad que los que no recibieron nebulizaciones, sin encontrarse diferencias en la necesidad de cambiar a modalidad con doble nivel de presión. En los pacientes con MFT la estancia en UCIP fue menor ( $p = 0,033$ ) a pesar de no existir diferencias en el nivel de gravedad; la tasa de fallo de VNI fue mayor en los que no recibieron nebulizaciones ( $p = 0,024$ ).

**Conclusiones:** La probabilidad de tener un efecto adverso relacionado con la nebulización es baja utilizando casco o MFT. La terapia inhalada con MFT puede disminuir la estancia en UCIP en algunos pacientes.

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## Introduction

In recent years, the use of non-invasive ventilation (NIV) in neonatal and pediatric intensive care units (NICU and PICU) settings has increased.<sup>1</sup> The use of NIV reduces length of stay and hospitalization costs<sup>2</sup> while improving patient comfort.

Helmet and total face mask (TFM) are two of the types of interfaces whose use in infants has been expanding in recent years. They offer several advantages in comparison with oronasal masks, such as fewer leaks, related to incorrect fitting of the interface or opening of the mouth, prevention of damage to the nasal mucosa and allowing modifications to fit the heads of younger children, as well as a high level of humidification.<sup>3</sup>

Several authors have reported good results with the use of Helmet and TFM in adult patients with acute respiratory

failure (ARF).<sup>4-6</sup> Better adaptation, less complications and similar efficacy to other interfaces have been described.<sup>5,7</sup> In children, the helmet has been used in patients with hypoxemic ARF, leukemia and in preterm neonates, but there are no reports of the use of TFM in children.<sup>3,8,9</sup>

Many pediatric patients need nebulized drugs. In fact, asthma and bronchiolitis are two of the main three leading causes of NIV usage.<sup>8</sup> Aerosol therapy for treatment of acute or acute-on-chronic respiratory failure in this setting may be delivered by pressurized metered-dose inhaler (pMDI) with a spacer and facemask, or nebulizer and facemask.

The use of nebulized drugs in patients treated with TFM and helmet is controversial because of the possibility of adverse effects, such as anisocoria due to nebulized ipratropium bromide.<sup>10,11</sup>

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The effectiveness of the nebulization depends on several factors (drug characteristics, airways anatomy, patient's inhalation technique and nebulization system). There are three types of devices for nebulized drugs: ultrasonic, pneumatic (jet type) and membrane type. The particles with a mass from 1 to 5  $\mu\text{m}$  are those that are more likely to reach the most appropriate site of the bronchial Tree.<sup>12</sup> Regarding the location of the nebulization system, results are very different; some authors obtain better results placing it between the interface and the leak port, while for others it is more effective to place it between the exhalation port and the ventilator for NIV.<sup>13,14</sup>

Therefore, the aim of our study was to evaluate the safety of aerosol therapy and his effect in infants using a helmet and TFM interfaces.

## Patients and methods

### Ethical considerations

The study was approved by the ethics committee of our hospital. On the admission to PICU an informed consent is given to all parents with the treatments they can receive according to medical criteria.

### Design

Descriptive analytical study of a prospective cohort.

### Sampling

By consecutive sampling, all patients admitted to the PICU requiring NIV with helmet or TFM in the PICU over a 29-month period (November 2013 to March 2016) were included. No patients were excluded.

### Methods

Interfaces used were: helmet StarMed (Intersurgical<sup>®</sup>) and total full face mask PerforMax (Philips<sup>®</sup>).

Although in the StarMed technical information, the possibility of using nebulized medication is mentioned without having to disconnect the patient, in the case of the PerforMax this is not mentioned on its label. However, there is a specific elbow to the nebulizer that is compatible with this mask, so its use would not be contraindicated.

The decision to add nebulized treatment was made according to medical criteria (fundamentally depending on the diagnosis and the presence of bronchospasm at pulmonary auscultation), and clinical practice guidelines of the unit. Frequency of administration of medication was established according to clinical severity (usually in a range between every 2 and 6 h) and was removed when it was not necessary (in PICU or outside) or no clinical response was observed.

Vibrating mesh (AeroNeb<sup>®</sup>) and jet nebulizers were used depending on availability in the unit and they were placed close to the patient (either between the leak port and the interface or 15–30 cm proximal to the leak port).

Jet nebulizer was filled with a solution of 5 ml and it was driven with oxygen at 6–8 liters per minute.

### Variables

The following independent variables were collected in every patient: age, sex, diagnosis, disease severity (using Wood Downes Ferrés – WDF – score, calculated at the moment of admission in PICU, in patients diagnosed with asthma and bronchiolitis), ventilation parameters and the use and type of nebulized drugs (if administered).

The main outcome of our analysis was the appearance of any side effects of nebulized drugs. A failure of NIV was considered when it was necessary to change from CPAP to bilevel mode or the need for intubation. Secondary outcomes were the failure of NIV, the evolution of disease severity (measured again using WD score), the duration of NIV, and length of stay in PICU.

### Statistical analysis

All data were collected prospectively in a national data base (NIV-research) supported by the Spanish Respiratory Working Group of the Spanish Paediatric Intensive Care Society, and analyzed with R (with R-commander) and Epidat 4.1 software.

Descriptive statistics in continuous variables were done with percentiles (median and interquartile range, IQR) and in discrete ones with percentages. In both cases population 95% Confidence Intervals were used. When there were zero counts in the numerator of percentages, posterior high density 95% probability intervals using Bayesian descriptive analysis were calculated, based on conjugated Beta-Binomial model with Beta ( $\frac{1}{2}$ ,  $\frac{1}{2}$ ) non-informative prior.

The statistical analysis was done in discrete variables with Fisher-Exact test and in continuous variables with Mann-Whitney *U* test, accepting  $p \leq 0.05$  as the significance level.

For the multivariate analysis, the patients were divided in two different cohorts based on NIV interface used. In both, TFM and Helmet cohorts, multivariate Logistic or Cox regression models were fitted using Akaike Informative Criteria (AIC).

### Results

The study sample consisted of 152 children treated with helmet or TFM. 61 patients received aerosol therapy during the NIV. The median age was 3.7 months (IQR 1.6–17.1). The most frequent diagnoses were bronchiolitis (60.5%), asthma/bronchospasm (20.4%) and pneumonia (9.9%). Thirty percent were younger than 57 days.

If we study the diagnostics according to de type of interface, 63 patients (90%) with a helmet and 29 patients (35.4%) with TFM, have a bronchiolitis. The rest of patients who wear TFM have asthma or bronchospasm (36.5%) and pneumonia (17.1%). These differences in the type of pathology explain why the median age and weight are lower in patients with

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**Table 1** Characteristics of patients and interface used.

	TFM	Helmet	Total
N	82	70	152
Age <sup>a</sup> (months)	15.6 (IQR 6.5–42.2)	1.7 (IQR 1.2–3.1)	3.7 (IQR 1.6–17.1)
Weight <sup>a</sup> (kg)	10 (IQR 7–15)	4 (IQR 3–5)	6 (IQR 4–11)
PICU hospitalization <sup>a</sup> (days)	4 (IQR 2–6.2)	6 (IQR 4–8)	5 (IQR 3–8)
NIV (hours) <sup>a</sup>	38.5 (IQR 20–66.1)	48 (IQR 31–83)	43 (IQR 23.6–74.3)
Diagnosics	Bronchiolitis 29 (35.4%) Asthma/bronchospasm 30 (36.5%) Pneumonia 14 (17.1%) Apneas 1 (1.2%) Others 5 (6.1%)	Bronchiolitis 63 (90%) Bronchospasm 1 (1.4%) Pneumonia 1 (1.4%) Apneas 4 (5.7%) Others 1 (1.4%)	Bronchiolitis 92 (60.5%) Asthma/bronchospasm 31 (20.4%) Pneumonia 15 (9.9%) Apneas 3 (3.3%) Others 6 (3.9%)
Nebulization	44 (53.7%)	17 (24.3%)	61 (40.1%)
Salbutamol	10 (22.7%) (N = 44)	6 (35.3%) (N = 17)	16 (26.2%) (N = 61)
Salbutamol and Ipratropium	34 (77%) (N = 44)	0 (N = 17)	34 (55.7%) (N = 61)
Epinephrine	0 (N = 44)	12 (70.6%) (N = 17)	12 (19.7%) (N = 61)
Intubation rate	4 (4.9%)	1 (1.4%)	5 (3.3%)
Paliative NIV	2 (2.4%)	0	2 (1.3%)

<sup>a</sup> Age, weight, PICU hospitalization and duration of NIV are expressed as median. PICU: pediatric intensive care unit; NIV: non-invasive ventilation; TFM: total face mask. N: number of patients receiving nebulized drugs.

helmet (1.7 months, 4 kg) compared to patients with TFM (15.6 months, 10 kg).

The median length of stay in the PICU was 5 days (IQR 3–8). The median duration of ventilation was 43 h

(IQR 23.6–74.3). Characteristics of patients are shown in [Tables 1 and 2](#).

Analyzing separately the groups according to the interface, as can be seen in [Table 3](#), in patients with helmet there

**Table 2** Characteristics of patients according to the use of nebulized drugs.

	With aerosol therapy (61)	Without aerosol therapy (91)	p-Value
Age <sup>a</sup> (months)	14 (IQR 3.6–36.8)	2.3 (IQR 1.3–6.9)	0 .003
Weight <sup>a</sup> (kg)	10 (IQR 5–14)	5 (IQR 4–7)	0 .001
Days in PICU <sup>a</sup>	4 (IQR 3–8)	5 (IQR 3–7)	0 .396
Hours NIV <sup>a</sup>	37 (IQR 20–65.3)	48 (IQR 26–84)	0 .127
Change to invasive MV	0 (0%)	5 (5.5%)	0 .001
Helmet	17 (27.9%)	53 (58.2%)	
TFM	44 (72.1%)	38 (41.8%)	
Diagnosics	Asthma/Bronchospasm 34 (55.8%) Bronchiolitis 26 (42.6%) Others 1 (1.6%)	Bronchiolitis 66 (72.5%) Pneumonia 11 (12.1%) Apneas 4 (4.4%) Asthma/Bronchospasm 3 (3.3%) Others 7 (7.7%)	

<sup>a</sup> Age, weight, days in PICU and hours of NIV are expressed as median. PICU: pediatric intensive care unit; NIV: non-invasive ventilation; MV: invasive mechanical ventilation; TFM: total face mask; kg: kilograms.

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**Table 3** Comparison between patients with or without nebulized drugs according to the type of interface.

	With aerosol therapy	Without aerosol therapy	p-Value
HELMET (N = 70)	17 (24.29%)	53 (75.71%)	
Age <sup>a</sup> (months)	2.8 (IQR 1.4–3.6)	1.6 (IQR 1.1–2.9)	0.431
Weight (kilograms)	4 (IQR 3–5)	4 (IQR 3–5)	0.363
WD Score	10 (IQR 8–12)	8 (IQR 6–9)	0.008
Days in PICU <sup>a</sup>	8 (IQR 6.5–16.5)	5 (IQR 3–7)	0.046
Hours NIV <sup>a</sup>	60 (IQR 34.5–83)	48 (IQR 31–82)	0.714
Failure (BLPAP NIV)	3 (4.3%)	12 (17.14%)	0.760
TFM (N = 82)	44 (53.7%)	38 (46.34%)	
Age (months) <sup>a</sup>	22.5 (IQR 12–47.1)	7.4 (IQR 3.3–39.9)	0.228
Weight (kilograms)	12 (IQR 9–15)	7.5 (IQR 4.8–14)	0.032
WD Score	8 (IQR 8–10)	8 (IQR 6–9)	0.071
Days in PICU <sup>a</sup>	3 (IQR 2–5)	5 (IQR 3–9.5)	0.033
Hours NIV <sup>a</sup>	31.5 (IQR 20–51.1)	46.5 (IQR 23.1–91.1)	0.076
NIV Failure (Intubation)	0 (0%)	4 (4.9%)	0.024

<sup>a</sup> Age, Weight, Wood Downes Score on admission in PICU, Days in PICU and Hours of NIV are expressed as median. IQR: interquartile range. Percentages are relative to the total number of patients with the same interface (helmet/TFM).

PICU: pediatric intensive care unit; NIV: non-invasive ventilation; WD: Wood Downes score; BLPAP: bilevel positive airway pressure; TFM: total face mask.

are statistically significant differences in severity of WD score and length of stay in PICU between the group receiving aerosol therapy and the non-aerosol group ( $p = 0.008$  and  $p = 0.046$  respectively).

No side-effects due to drugs were observed. If Bayesian statistic is applied the probability of having an adverse effect is 1.3% with helmet (probability interval = 0.000–0.135) and with TFM 0.5% (probability interval = 0.000–0.055).

Using multivariate analysis and Cox regression (Tables 3 and 4), it can be observed that with helmet, nebulized therapy is used in the more severe cases and this use does not affect the failure rate nor the length of stay in PICU. Nevertheless, with TFM nebulized therapy is used

in older patients and this use shortens the length of stay in PICU without affecting the failure rate.

However, if intubated or patients who died are excluded, no statistical differences are observed in the median of length of stay in patients with or without nebulized drugs (4 days with nebulized treatment, 5 days without inhaled drugs,  $p = 0.99$ ).

## Discussion

The increasing use of NIV in pediatric population, together with the need to associate inhaled drugs in a high percentage of cases (40.1%), makes this an important issue.

**Table 4** Logistic regression and Cox regression studies according to the type of interface.

		Logistic regression: failure NIV (BLPAP use)		
		Odds ratio	95% CI	p-Value
HELMET	Intercept	1.00	0.084–11.0	1
	Score WD	0.85	0.62–1.18	0.345
	Nebulization	1.3	0.24–7.1	0.76
	Cox regression: days in PICU	Nebulization: $p = 0.51$		
Score WD: $p = 0.407$				
		Logistic regression: failure NIV (Intubation)		
		Odds ratio	95% CI	p-Value
TFM	Intercept	0.105	0.03 to 0.38	0.00059
	Age (months)	1.02	0.994 to 1.05	0.136
	Nebulization	5.55e–09	0.000 to Infinity	0.994
	Cox regression: days in PICU	Nebulization: HR (95CI) = 1.7 (1.07–2, $p = 0.019$ )		
Age (months): $p = 0.457$				

NIV: non-invasive ventilation; CI: confidence interval; HR: hazard ratio; TFM: total face mask; WD: Wood Downes score on admission in PICU; PICU: pediatric intensive care unit.

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Although side effects with nebulized drugs in patients with face masks have been published,<sup>11</sup> our cases appear to confirm that side effects are an extremely infrequent event.

The most important finding is that in our study the use of inhaled therapy with TFM (if required), reduces hospital stay without side-effects (61% of patients receiving these drugs have asthma). However, with helmet, it has no effect on failure or hospital stay (94% of the patients in which inhaled drugs were used presented with bronchiolitis).

Otherwise it is important to note that to our knowledge, this is the first report of use of TFM in children.

Nevertheless, our study has limitations. The main limitation is that it is a descriptive study and we do not have any control group to compare with.

The importance of nebulization as adjunctive therapy to ventilation (although not recommended in the latest guidelines of bronchiolitis – NICE guide –), the low frequency of adverse events related to its use and the minor clinical consequences, allows us to recommend the use of nebulized drugs, if necessary (for example in asthma and bronchospasm), when a patient uses a TFM or a helmet.

In conclusion, the probability of a pediatric patient having an adverse effect related to nebulization is extremely low using helmet or Total Face Mask. In our experience, aerosol therapy with helmet or TFM is safe and can reduce hospital stay in some patients.

## Authors contributions

- Lucía Rodríguez García: Study design, acquisition, analysis and interpretation of data. Preparation of the draft of the article. Final approval of the presented version.
- Alberto Medina Villanueva: Study design, acquisition, analysis and interpretation of data. Preparation of the draft of the article and critical review of it. Final approval of the presented version.
- Vicent Modesto i Alapont. Study design, analysis and interpretation of data. Article review. Final approval of the presented version.
- María Luisa Palacios Loro. Acquisition of data, critical review of the content of the article. Final approval of the presented version.
- Juan Mayordomo-Colunga. Analysis and interpretation of data. Article review. Final approval of the presented version.
- Ana Vivanco Allende. Analysis and interpretation of data. Article review. Final approval of the presented version.
- Corsino Rey Galán. Analysis and interpretation of data. Article review. Final approval of the presented version.

## Conflict of interests

Authors have no conflict of interests to declare.

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