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Prehospital β&;-agonist administration via spacer versus nebuliser

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ABSTRACT

INTRODUCTION. In 2021, administration of β&;-agonist in the ambulance changed from nebuliser to spacer in the North Denmark Region. We aimed to quantify the effectiveness of the switch by comparing 1) dyspnoea score, 2) median pCO_2, pH, and paO_2 and 3) vital signs.

METHODS. We conducted a quality assessment study including adults treated in the ambulance with a β&;-agonist from 2018 to 2022 in the North Denmark Region. Prehospital vital signs, dyspnoea scores (0-10) and medicine administration data were collected from the electronic prehospital medical record. Blood gas analyses were collected from the clinical laboratory information system.

RESULTS. A total of 6,521 patient encounters were included, 70% received β&;-agonist by nebuliser and 30% by spacer. Dyspnoea scores were recorded in 45%, arterial blood gas analysis in 62%. The median (interquartile range) last dyspnoea score was 4 (3-6) in both groups, $p = 0.79$. The nebuliser group had a higher median $paCO_2$ (6.0 versus 5.8, $p < 0.001$), a lower pH (7.38 versus 7.40, $p < 0.001$), a higher paO_2 (9.20 versus 9.00, $p < 0.001$), and a higher last measured mean pulse (99 versus 97, $p = 0.001$) than the spacer group.

CONCLUSIONS. Patients receiving β&;-agonist by spacer had similar relief of dyspnoea as those who received the medicine by nebuliser. Patients using the nebuliser had a higher median $paCO_2$, a lower pH and a higher pulse rate than patients using the spacer.

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TRIAL REGISTRATION. Hospitals and prehospital administration approval no. 2017-011259. Data collection registration no. K2022-073.

Respiratory emergencies, including exacerbations of asthma and chronic obstructive pulmonary disease (COPD), are common reasons for prehospital medical care and ambulance transport in Denmark [1]. Effective management of these emergencies is critical to ensuring positive patient outcomes and minimising morbidity and mortality. β&;-agonists, such as salbutamol, are widely used in treating respiratory emergencies owing to their bronchodilatory effects that alleviate respiratory distress [2]. During the coronavirus disease (COVID-19) pandemic, healthcare providers faced numerous challenges, including concerns about the potential for aerosol generation and virus transmission while administering nebulised medications [3]. In response to these concerns,

the North Denmark Region changed the administration of β&;-agonists in ambulances from oxygen-powered nebulisers to pressurised metered-dose inhalers with a holding chamber (spacers) in 2021. In addition to minimising the risk of infection, the spacer allows bronchodilator drugs to be administered without accompanying oxygen therapy (oxygen is the only compressed gas available in the ambulances). This may be of particular importance in patients with COPD, where excessive oxygen levels may result in hypercapnic respiratory failure [4]. While both nebulisers and spacers are effective methods for delivering β&;-agonists [5-8], it remains unclear whether the change in administration method impacts patient dyspnoea and physiological parameters in a prehospital setting. This study aimed to quantify the effect of switching from nebulisers to spacers in a prehospital setting. The primary outcome of interest was the last measured dyspnoea score in the ambulance before arrival at the hospital, indicating the prehospital treatment's effectiveness in alleviating respiratory discomfort. Secondary outcomes were median pCO_2, pH and paO_2 values, and vital signs (respiratory frequency, saturation, pulse and the Glasgow Coma Scale (GCS)).

MethodS

Study design and setting

We conducted a quality assessment study in the North Denmark Region from April 2018 through October 2022. The study area spanned 7,884 km^2 and comprised a mixed urban/rural population of 0.6 million [9]. In Denmark, tax-funded healthcare is provided for all citizens free of charge at the point of care. Ambulances were operated by two basic life-support (BLS)– or advanced life-support (ALS) paramedics. To treat dyspnoea, BLS paramedics could provide oxygen and inhaled β&;-agonists. In addition, ALS paramedics could provide inhaled β&;-agonists in combination with anticholinergics and apply continuous positive airway pressure (O2-MAX, Pulmodyne). Before 1 April 2021, bronchodilating medications were given by oxygen-driven nebulisers (2.5 mg salbutamol per dose). As of 1 April 2021, the administration device for providing inhaled bronchodilators was gradually changed to pressurised metered-dose inhalers with a holding chamber (spacers) (0.1 mg salbutamol per dose), allowing ambulances to use up their stores of nebulisers. All vehicles had tablet-based electronic patient records (Amphi, Dedalus, Denmark).

Ethics

This quality assessment study was approved by the hospital and prehospital administration (no. 2017-011259), granting permission to access patient data without patient consent. The data collection was registered as a quality assessment study in the North Denmark Region (no.: K2022-073). Danish law did not require permission from the Ethics Committee as this was a quality study.

Data sources

Data were obtained from the electronic prehospital and in-hospital records and from clinical laboratory databases (Labka). All Danish citizens are assigned a unique personal identification number, which allows for crosslinking of records between institutions (e.g. prehospital charts, hospital charts and biochemistry reports) [10].

Study population

The study population included all encounters with adult patients (≥ 18 years) who received β&;-agonist treatment in the prehospital setting, either by nebuliser or spacer, during the study period. Patient encounters were excluded if a β&;-agonist was received by both nebuliser and spacer.

Variables

Dyspnoea score

The dyspnoea score was an ordinal integer scale ranging from zero to ten, with zero indicating no difficulties breathing and ten representing the worst possible dyspnoea. Paramedics were encouraged to note the dyspnoea score during the primary assessment of the patient and again immediately before arrival at the hospital or if the patient was treated and released on scene [11]. The first and last recorded dyspnoea scores were collected.

Vital signs

Vital signs measurements from LIFEPAK 15 (Physio Control/Stryker) or Zoll X Series (Zoll, an Asahi Kasei company) monitors were automatically transmitted to the prehospital medical records, and manual measurements were entered in the records by the ambulance personnel. We obtained the first and last measured values regarding oxygen saturation, respiratory rate, pulse, GCS and temperature in the ambulance. Manual measurements of respiratory frequency were preferred if available. Clinically implausible vital sign measurements and measurements outside the range of the equipment (LIFEPAK 15 and ZOLL X Series) were excluded (saturation measurements were excluded below 60%, respiratory rate above 100/min., pulse below 25 or above 240 beats/min. if automatically measured. If measured manually, values above 300 were excluded. Furthermore, temperatures below 12 or above 43 degrees Celsius were excluded).

Blood gas analysis

The first blood gas analysis made after arrival at the hospital was obtained, and the time stamp was noted. The blood gas was considered relevant within six hours from arrival at hospital. We included arterial and venous samples (V-GAS). If a venous-to-arterial conversion (V-TAC) was made, those values were also collected [12]. We included pH, pCO_2 and paO_2 values.

Outcomes

The primary outcome of interest was the last measured dyspnoea score. Secondary outcomes were median pCO_2, pH, paO_2 values and vital signs. Furthermore, a post-hoc analysis was conducted on the risk of fulfilling biochemical criteria for non-invasive ventilation [13].

Statistical analysis

Mean and standard deviation were used for normally distributed data; median and interquartile range (IQR), for non-normal distributed data. Normal distribution was visually assessed with histograms and quantile-quantile plots. A proportional odds model adjusting for the first dyspnoea score, sex and age was used to assess the administration effect on the last measured dyspnoea score. Between-group vital signs, pCO_2, pH and paO_2 between groups were compared by the Mann-Whitney test or the t-test. Missing data were omitted from their related analysis. The proportion of missing values for each analysed variable and the types of subjects with missing variables were described. Data were anonymised before analysis; one patient may contribute multiple analysis episodes. R was used for statistical analysis [14].

Trial registration: Hospitals and prehospital administration approval (no. 2017-011259). Data collection registration (no. K2022-073).

Results

During the study period, β&;-agonists were administered at 6,788 patient encounters. A total of 267 patient encounters were excluded (227 were below 18 years of age, nine were of unknown age and 31 received β&;-agonist by both spacer and nebuliser) (**Table 1**).

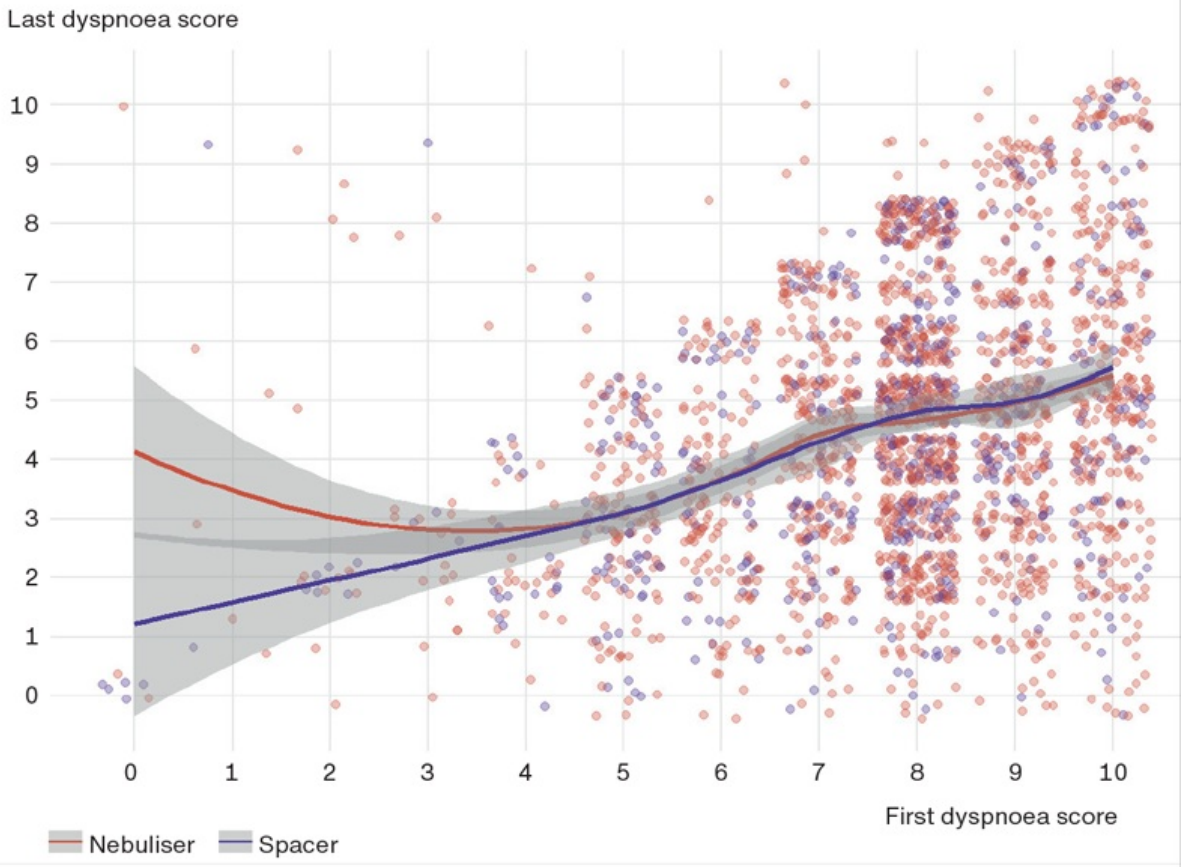
TABLE 1 Characteristics of the study group.

	Nebuliser (N_{neb} = 4,578 (70%))	Spacer (N_{spa} = 1,943 (30%))	Overall (N_{tot} = 6,521)
Age, median (IQR), yrs	74 (65-81)	76 (66-82)	74 (65-81)
Female sex, n (%)	2,440 (53.3)	1,046 (53.8)	3,486 (53.5)
Measured dyspnoea score, n (%)	2,190 (48)	734 (38)	2,924 (45)
Measured once	457	175	632
Measured > 1 ×	1,733	559	2,292
Blood gas analyses within 6 hrs, n (%)	4,185 (91)	1,741 (90)	5,926 (91)
Arterial blood gas	2,879 (63)	1,166 (60)	4,045 (62)
Venous blood gas	1,306 (29)	575 (30)	1,881 (29)
V-TAC	680 (15)	169 (8.7)	849 (13)
Vital values, n (%)			
Respiration frequency	4,400 (96)	1,902 (98)	6,302 (97)
Saturation	4,523 (99)	1,931 (99)	6,454 (99)
Pulse	4,529 (99)	1,932 (99)	6,461 (99)
GCS	4,411 (96)	1,874 (96)	6,285 (96)
Temperature	3,442 (75)	1,601 (82)	5,043 (77)
Administered medicine, n (%)			
Salbutamol	4,559 (99.6)	1,943 (100.0)	6,502 (99.7)
Salbutamol + ipratropium	32 (0.7)	0	32 (0.5)
Doses of salbutamol, median (IQR), n	2 (2-4)	2 (1-3)	2 (2-3)

GCS = Glasgow Coma Scale; IQR = interquartile range; V-TAC = venous to arterial conversion.

The groups did not differ significantly concerning sex distribution, but the spacer group was slightly older than the nebuliser group (two years) (Table 1). The median (IQR) of the first dyspnoea score was 8 (7-9), and the median (IQR) of the last dyspnoea score was 4 (3-6) in both the spacer and nebuliser groups. No significant dyspnoea score difference was recorded in the multivariable model adjusting for sex, age and first dyspnoea score, p = 0.79 (**Figure 1**).

FIGURE 1 Association between last and first recorded dyspnoea score in patients treated with β_2-agonist administered by nebuliser or spacer. The points show the measured dyspnoea score (the x-axis is the first score and the y-axis the last score). The lines indicate locally estimated scatterplot smoothing of the average last dyspnoea score for each start dyspnoea score, with a confidence interval shown in grey. There was no significant difference between nebuliser- and spacer-treated patients, p = 0.79 by regression. Points are jittered to reduce overplotting.



The spacer group had a significantly lower median $paCO_2$ (5.8 versus 6.0, $p < 0.001$), a higher pH (7.40 versus 7.38, $p < 0.001$) and a lower paO_2 (9.00 versus 9.20, $p < 0.001$) than the nebuliser group. The difference in arterial oxygen level was rooted in high values in the nebuliser group, and the distribution of hypoxia was similar between the groups (see Supplementary Figure 1). No differences were observed between the V-TAC or V-Gas of the groups (see **Table 2**). The post-hoc analysis of risk for fulfilled biochemical criteria for non-invasive ventilation showed a higher risk in the nebuliser group (see Supplementary Figure 2) [13].

TABLE 2 Blood gas and vital values.

	Nebuliser (N_{neb} = 4,578)	Spacer (N_{spa} = 1,943)	Overall (N_{tot} = 6,521)	p value	Missing, %
With a blood gas, n	4,185	1,741	5,926		
Patient's O_2 flow[a], median (IQR), l/min.	3.00 (2.00-7.00)	2.00 (1.00-3.50)	3.00 (2.00-6.00)	< 0.001	59.4
P-arterial blood, median (IQR)					
pH	7.38 (7.31-7.43)	7.40 (7.34-7.44)	7.38 (7.32-7.43)	< 0.001	32.1
pCO_2, kPa	6.00 (5.00-7.80)	5.80 (4.90-7.30)	5.90 (5.00-7.70)	< 0.001	31.8
pO_2, kPa	9.20 (7.90-11.40)	9.00 (7.80-10.30)	9.10 (7.90-11.10)	< 0.001	31.8
P-venous blood, median (IQR)					
pH	7.37 (7.33-7.41)	7.38 (7.34-7.41)	7.37 (7.34-7.41)	0.192	68.3
pCO_2, kPa	6.40 (5.50-7.60)	6.30 (5.50-7.30)	6.30 (5.50-7.50)	0.081	68.3
pO_2, kPa	4.70 (3.80-5.95)	4.50 (3.48-5.82)	4.60 (3.70-5.90)	0.178	85.2
Venous to arterial conversion, 37 °C[b]:					
pH	7.41 (7.37-7.44)	7.41 (7.38-7.44)	7.41 (7.37-7.44)	0.864	85.7
pCO_2, kPa	5.40 (4.80-6.50)	5.30 (4.70-6.40)	5.40 (4.70-6.50)	0.448	85.7
pO_2, kPa	10.00 (8.90-10.00)	10.00 (9.10-10.00)	10.00 (8.90-10.00)	0.780	85.7
Respiratory rate, median (IQR), breaths/min.					
First[c]	26 (22-30)	26 (22-30)	26 (22-30)	0.454	3.4
Last[d]	24 (20-28)	24 (20-)	24 (20-28)	0.676	3.4
Difference[e]	1.00 (0.00-5.00)	0.00 (0.00-4.00)	1.00 (0.00-5.00)	0.371	3.4
O_2 saturation, median (IQR), %					
First[c]	92 (84-96)	90 (83-95)	91 (84-96)	< 0.001	4.1
Last[d]	96 (92-98)	95 (92-97)	95 (92-98)	< 0.001	1.3
Difference[e]	−4 (−9-0)	−4 (−10, 0)	−4 (−10-0)	0.002	4.4
Pulse, median (± SD), beats/min.					
First[c]	101.21 (± 22.95)	100.43 (± 24.08)	100.98 (± 23.29)	0.215	0.9
Last[d]	99.23 (± 21.77)	97.31 (± 21.98)	98.66 (± 21.85)	0.001	1.9
Difference[e]	1.95 (± 19.89)	3.07 (± 22.02)	2.29(± 20.55)	0.046	2.0
GCS score, median (IQR)					
First[c]	15 (15-15)	15 (15-15)	15 (15-15)	< 0.001	3.6
Last[d]	15 (15-15)	15 (15-15)	15 (15-15)	< 0.001	3.6
Difference[e]	0 (0-0)	0 (0-0)	0 (0-0)	0.590	3.6
Temperature, median (IQR), °C	36.80 (36.50-37.60)	36.70 (36.40-37.30)	36.80 (36.50-37.50)	< 0.001	22.7

GCS = Glasgow Coma Scale; IQR = interquartile range; SD = standard deviation.
a) At the time of the test.
b) Assuming a temperature of 37 °C.
c) First measured value by the ambulance upon arrival to the patients.
d) Last measured value by the ambulance before handover at the hospital or if the patient was treated and released on scene.
e) Difference between first and last measured value.

Vital values in the two groups were mostly similar, but a slight difference was recorded in the last measured mean pulse and the last measured saturation (Table 2).

Discussion

This quality assessment study showed that the patients who received β&;-agonist by spacer had similar relief of dyspnoea as patients who received the medicine by nebuliser. Similar conclusions on symptom relief have previously been documented [7, 15]. The spacer group had a more favourable arterial blood gas and a lower pulse rate than the nebuliser group, which indicated fewer side effects. These findings align with guidelines [2] and previous studies, which either found the two administration routes to be comparable or tended to prefer the spacer [2, 5, 7, 15, 16]. Previous research, however, was mostly conducted in primary care, emergency departments or during hospitalisation [8]. To our knowledge, this study is the first to compare the treatment effects of spacers and nebulisers in the prehospital setting.

For the primary outcome, a self-reported dyspnoea score was used to evaluate subjective treatment effect,

finding similar results in the two groups. There is, however, a potential risk that the most severely affected patients were too ill to convey a dyspnoea score [17]. This could potentially cause missing values.

A slight difference in pulse rate (two beats/min.) was found. The group that received the medicine by spacer had a lower pulse than the group that received it by nebulisation. Though the difference is statistically significant, it probably has no clinical consequence. This finding is in agreement with previous reports [5, 8]. One explanation may be better active drug delivery to peripheral lung tissue; hence, lower dosage and fewer side effects [18].

In this study, a lower paO_2 was observed in the spacer group than in the nebuliser group. This difference is well explained by the fact that patients in the nebuliser group received a fixed oxygen flow of 6-8 l/min. to drive the nebuliser because oxygen was the only compressed gas available onboard the ambulance. In contrast, patients in the spacer group could be treated without receiving supplementary oxygen. On the same note, high oxygen levels may reduce the respiratory drive in patients with COPD, leading to increased levels of arterial carbon dioxide. This may potentially explain the finding of increased $paCO_2$, and consequently lower pH, in the nebuliser group.

A major strength of this study is its population-based design, which minimises selection bias and increases generalisability. Furthermore, the study was conducted within a uniform, tax-funded healthcare system, thereby minimising the risk of selection bias. Another strength is the number of patient encounters included and the amount of blood gases available for analysis. The fully digitalised pre- and in-hospital patient record systems and laboratory databases, and the ability to crosslink these using the Civil Registration System, provide a unique opportunity to investigate the effects of prehospital treatment [10, 19].

The present study also has some limitations. The spacer and the nebuliser group had some missing data, especially on dyspnoea scores and arterial blood gases. This may potentially lead to bias if unbalanced between groups or related to outcome measurements. There were fewer missing dyspnoea scores in the spacer group, probably due to information campaigns about the project and the spacer. No difference was observed between missing data on the secondary outcome. Another limitation is the before-and-after design, which imposes a risk of confounding the case-mix changes over time. During the study period, COVID-19 infection contributed to aggravating COPD and asthma. Also, governmental initiatives were launched to avoid admission of those with less severe disease to relieve strain on the hospital system. This would likely cause the participants in the later years of the study period to have a higher disease burden. In concordance, the patients in the spacer group were older than those in the nebuliser group. This might have reduced the measured effect in the spacer group compared with the nebuliser group. Another factor that might have reduced the effect of the spacer group is the time interval for measuring blood gases (six hours).

Conclusions

This quality assessment study of patients treated with inhaled β_2-agonists in the prehospital setting shows similar dyspnoea relief in patients who received treatment by spacer and patients to whom medication was delivered via a nebuliser. Patients using the nebuliser had a higher median $paCO_2$, a lower pH and a higher pulse rate than patients using the spacer. Our study showed no sign of reduced quality in prehospital treatment of dyspnoea following the transition from nebuliser to spacer as the delivery device for bronchodilators. If any difference exists, treatment with spacers seems to be favourable. These findings, in conjunction with the theoretical advantages regarding a lower risk of spreading infectious organisms, and the ability to titrate oxygen therapy with a spacer compared to a nebuliser, point towards preferring spacers for prehospital β&;-agonist treatment. We cannot, however, determine whether one of the two delivery systems is superior to the other due to the observational design of our study. We therefore encourage future prehospital studies to compare

treatment with spacers and nebulisers in a randomised study.

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