Original paper

A comparison of the costs of bronchodilator delivery methods in children with asthma exacerbations treated in hospital. The first Polish study in children

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Adv Dermatol Allergol 2021; XXXVIII (6): 1011–1016
DOI: https://doi.org/10.5114/ada.2020.98131

Abstract

Introduction: Recommended methods of administering bronchodilator drugs in children with asthma exacerbations in a hospital include the pressurized metered-dose inhaler (pMDI) and nebulization (NEB). These methods differ in clinical effectiveness, safety and, as some studies indicate, the cost of their use in a child.

Aim: To calculate the direct costs of hospital therapy conducted with the use of short-acting β_2-agonist (SABA) or its combination with short-acting muscarinic antagonist (SAMA) administered via pMDI with valved holding chamber (VHC) versus the same drugs in NEB in children with asthma exacerbation.

Material and methods: A retrospective analysis of the costs of SABA (salbutamol) and SABA + SAMA (fenoterol + ipratropium bromide) inhalation therapy was performed. Based on the data obtained from the financial department, the pharmacy, and the sterilization department of the university hospital, the direct unit cost of the inhalation therapy in the child was calculated.

Results: The results of the analysis indicate that in a hospital setting the cost of one-time SABA or SABA + SAMA administration via pMDI+VHC is 1.5–2.4 times lower compared to NEB. The payer incurred the lowest costs during anti-obstructive treatment using SABA with pMDI + VHC (PLN 9.39 for one inhalation procedure). The working time of medical staff during the inhalation treatment is the component generating the highest cost for the hospital (up to 40% of direct costs).

Conclusions: In hospital conditions, the supply of SABA or SABA + SAMA with the use of pMDI + VHC in a child with asthma exacerbation is more beneficial financially than the supply of the same drugs in NEB.

Key words: nebulization, pressurized metered-dose inhaler, bronchodilator, asthma, children.

Introduction

Short-acting β_2-agonists (SABA) or their combination with short-acting muscarinic antagonists (SAMA) in inhalation are among the most important anti-obstructive drugs. These drugs are used in many diseases with acute bronchial obstruction in children, such as asthma, bronchitis, bronchiolitis, bronchopulmonary dysplasia, and pulmonary exacerbation of cystic fibrosis. They are available in the following inhalation forms: pressurized metered-dose inhaler (pMDI), breath-actuated pressurized metered-dose inhaler (pMDI-BA), metered-dose liquid inhaler (MDLI), dry powder inhaler (DPI) and as solutions for nebulization (NEB) [1–6].

Rational health policy is based on pharmacoeconomic analyses. These analyses help in choosing the method of treatment of a given disease – which one is most cost-effective while maintaining the highest clinical effectiveness. Research to date has shown that SABA as well as the combination of SABA and SAMA used in aerosol therapy of respiratory diseases may differ not only in the method of administration, but also in clinical effectiveness, safety and costs associated with their use in patients [3, 7–9]. Research results indicate that regardless of the calculation method, the use of SABA with pMDI in combination with a valved holding chamber (VHC) instead of NEB is associated with a reduction in total costs in both the emergency department and the hospital ward [10–15]. There has been no similar analysis carried out in Poland.

Aim

The aim of the study was to estimate the total direct costs of bronchial obstruction therapy in children with

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Received: 28.06.2020, **accepted:** 13.07.2020.

asthma exacerbation using SABA or a combination of SABA and SAMA administered via pMDI + VHC versus the same drugs in NEB in a hospital ward setting.

Material and methods

An analysis was carried out of the costs of inhalation therapy SABA (salbutamol) and SABA (fenoterol) in combination with SAMA (ipratropium bromide) conducted in children with asthma exacerbation in a hospital setting from the payer's perspective. The direct costs of two inhalation therapy methods (pMDI + VHC, NEB) used in the non-invasive treatment wards of the University Children's Hospital in Lublin were calculated (in accordance with the hospital procedure for the administration of inhaled drugs number PPO7/2018) taking into account direct medical costs (cost of drugs, devices for their administration, remuneration for medical staff) as well as direct non-medical costs (cost of personal protective equipment, sterilization of drug delivery devices) [16, 17]. The sources of data necessary to calculate the above-mentioned costs are presented in Table 1.

The actual cost of one inhalation procedure was estimated for the doses of drugs recommended for an average child aged 6 years with bronchial obstruction, in whom bronchodilators were administered via pMDI + VHC (with a mouthpiece) or via a nebulizer through the mouthpiece according to current recommendations [5]. At the University Children's Hospital in Lublin, bronchodilator drugs are mainly delivered by VHC, such as AeroChamber Plus Flow-Vu® and RespiChamber Hospital® as well as by the OMRON A3 Complete® jet nebulizer and the Intec Twister Mesh® nebulizer. The technical characteristics of the tested inhalation devices are summarized in Table 2. The calculations also took into account drug losses during filling residual volume of nebulizers (RV). The average duration of the inhalation procedure was based on data from the Mason *et al.* study (Table 1), while the lifespan of inhalation drug delivery devices was adopted according to the manufacturer's recommendations [18].

Table 1. Output sources

Variables and model parameters	Data sources
Drug costs	Data obtained from the Pharmacy of the University Children's Hospital in Lublin (price list as of 21.04.2020)
The cost of valved holding chambers	The offer obtained from NZ Techno on 21.04.2020*
The cost of nebulizers	Data based on the purchase invoice of the OMRON A3 Complete® and Intec Twister Mesh® for the needs of one of the departments at the University Children's Hospital in Lublin (January 2020)
Sterilization cost	Data obtained from the Sterilization and Disinfection Department of the University Children's Hospital in Lublin (price list as of 21.04.2020)
Nurse's remuneration	Announcement of the Speaker of the Sejm of the Republic of Poland of 28 June 2019 regarding the publication of the consolidated text of the act on the method of determining the lowest basic salary of certain employees employed in health care entities
Time needed to complete the drug delivery procedure with the use of pMDI + VHC or NEB	Time and motion study by Mason *et al.* [18] and the measured real time needed to perform the inhalation procedure (3 min. for pMDI + VHC, 7 min for NEB with a mesh nebulizer, 20 min for NEB with a constant-output jet nebulizer)
The cost of additional materials necessary during the inhalation procedure (gloves, disinfectant, syringes, needles)	Data obtained from the hospital's financial department. Guidelines for the use of personal protective equipment in accordance with the in-hospital procedure "Inhalation medication using various aerosol therapy techniques" (procedure number: PPO7/2018)

*pMDI – pressurized metered-dose inhaler, VHC – valved holding chamber, NEB – nebulization; * main distributor of Trudell Medical International products in Poland.*

Table 2. Characteristics of tested devices used during the aerosol therapy

AeroChamber Plus Flow-Vu® – dual-valve, low-resistance, small-volume (149 ml), antistatic system, fitted to all pMDI, visual and acoustic control of the inspiratory flow rate
RespiChamber Hospital® – dual-valve, low-resistance, small-volume (149 ml), antistatic system, fitted to all pMDI, possibility of high-temperature sterilization
OMRON A3 Complete® – constant-output jet nebulizer, RV = 0.7 ml nebulization rate 0.3–0.7 ml/min MMAD of the aerosol cloud 3–10 µm
Intec Twister Mesh® – active mesh nebulizer, membrane reverse cleaning system, RV = 0.1 ml, MMAD of the aerosol cloud 4.8 µm, battery powered

pMDI – pressurized metered-dose inhaler, RV – residual volume, MMAD – mass median aerodynamic diameter.

Table 3. The cost of the drug and the device for its supply per inhalation procedure

Drug/medical device	Dose of the drug per inhalation procedure (excluding RV of the nebulizer)*	The cost of buying 1 pack of the drug or 1 medical device	Cost of the drug/medical device for one inhalation procedure (excluding the cost of the drug needed to fill the RV of the nebulizer)
Berodual® (NEB) (0.5 mg + 0.25 mg/ml)	0.38 mg + 0.19 mg (0.75 ml = 15 drops)	PLN 18.53 (20 ml)	PLN 0.70
Berodual N® (pMDI) (50 µg + 21 µg/puff)	100 µg + 42 µg (2 puffs)	PLN 25.86 (200 puffs)	PLN 0.26
Ventolin® (NEB) (1 mg/ml, 2.5 ml ampoules)	2.5 mg (1 ampoule)	PLN 14.18 (20 ampoules)	PLN 0.71
Ventolin® (pMDI) (100 µg/puff)	200 µg (2 puffs)	PLN 7.81 (200 puffs)	PLN 0.08
AeroChamber Plus Flow-Vu®	NA	PLN 60.48 (100 gas sterilizations)	PLN 0.61 + PLN 7.35 (gas sterilization)
RespiChamber Hospital®	NA	PLN 61.02 (100 gas sterilizations)	PLN 0.61 + PLN 7.35 (gas sterilization)
OMRON A3 Complete®	NA	PLN 150 (1000 inhalations)	PLN 0.15 + PLN 7.35 (gas sterilization)
Intec Twister Mesh®	NA	PLN 190 (1500 inhalations)	PLN 0.13 + PLN 5.25 (gas sterilization)

*pMDI – pressurized metered-dose inhaler, NEB – nebulization, RV – residual volume, NA – not applicable. *Based on the characteristics of the medicinal products (as of 20.04.2020).*

Table 4. Total direct cost of the inhalation procedure using a combination of short-acting β_2-agonists with short-acting muscarinic antagonists depending on the type of the inhalation device (in PLN)

Fenoterol + ipratropium bromide	Cost of the dose of medicine to be given to the patient	Cost of the drug needed to fill the RV of the nebulizer	Cost of one use of the medical device	Cost of additional materials (gloves, disinfectant)	Cost of a nurse's work	Cost of sterilization, packaging, hospital transport	Total direct cost of one inhalation procedure
OMRON A3 Complete® (RV = 0.7 ml) Drug: Berodual® (NEB)	0.70	0.65*	0.15	4.95	8.97	7.35	22.77
Intec Twister Mesh® (RV = 0.1 ml) Drug: Berodual® (NEB)	0.70	0.09**	0.13	4.95	3.14	5.25	14.26
pMDI + AeroChamber Plus Flow-Vu® Drug: Berodual N® (pMDI)	0.26	NA	0.61	0	1.35	7.35	9.57
pMDI + RespiChamber Hospital® Drug: Berodual N® (pMDI)	0.26	NA	0.61	0	1.35	7.35	9.57

*NEB – nebulization, pMDI – pressurized metered-dose inhaler, RV – residual volume, NA – not applicable. *The cost of 0.7 ml of Berodual. **The cost of 0.1 ml of Berodual.*

All costs were expressed in PLN and compared after converting the currencies with other analyses available in the literature.

Results

Based on the obtained data, the cost of inhalation drugs used in asthma exacerbation therapy and devices for their administration was calculated. According to the hospital price list of 21 April 2020, the payer paid PLN 0.08 for SABA and PLN 0.26 for SABA + SAMA administered via pMDI per inhalation procedure. The same drugs used in NEB cost the hospital PLN 0.71 and PLN 0.70 respectively (without taking into account the cost of the drug needed to fill the RV of nebulizer) and were 8.9 and 2.7 times more expensive than drugs administered by pMDI. Considering the lifetime of inhalation drug delivery devices, it was calculated that the cost of using VHC per treatment together with the costs of sterilization was PLN 7.96 (identical for both analysed VHC). When using nebulizers, these costs were lower and amounted to: PLN 7.50 for a jet nebulizer and PLN 5.38 for a mesh nebulizer (Table 3).

Table 5. The total direct cost of the inhalation procedure using short-acting β_2-agonists depending on the type of the inhalation device (in PLN)

Salbutamol	Cost of the dose of medicine to be given to the patient	Cost of the drug needed to fill the RV of the nebulizer	Cost of one use of the medical device	Cost of additional materials (gloves, disinfectant)	Cost of a nurse's work	Cost of sterilization, packaging, hospital transport	Total direct cost of one inhalation procedure
OMRON A3 Complete® (RV = 0.7 ml) Drug: Ventolin® (NEB)	0.71	0.71*	0.15	4.95	8.97	7.35	22.84
Intec Twister Mesh® (RV = 0.1 ml) Drug: Ventolin® (NEB)	0.71	0.71**	0.13	4.95	3.14	5.25	14.89
pMDI + AeroChamber Plus Flow-Vu® Drug: Ventolin® (pMDI)	0.08	NA	0.61	0	1.35	7.35	9.39
pMDI + RespiChamber Hospital® Drug: Ventolin® (pMDI)	0.08	NA	0.61	0	1.35	7.35	9.39

*NEB – nebulization, pMDI – pressurized metered-dose inhaler, RV – residual volume, NA – not applicable. *The cost of 1 ampoule of Ventolin®, of which 0.7 ml will be used to fill the RV of the nebulizer (drug loss = 1.8 ml). **The cost of 1 ampoule of Ventolin®, of which 0.1 ml will be used to fill the RV of the nebulizer (drug loss = 2.4 ml).*

Tables 4 and 5 present the actual costs of one inhalation procedure, taking into account the cost of the drug needed to fill the RV of the nebulizer, the cost of additional materials used, and the remuneration of medical staff. The cost of SABA + SAMA supply varied depending on the choice of the inhalation method. The hospital incurred the lowest expenses related to drug supply with pMDI + VHC – PLN 9.57. The cost of SABA+SAMA nebulization was 1.5-2.4 times higher (mesh nebulizer – PLN 14.26, jet nebulizer – PLN 22.77). The analysis of expenses related to SABA inhalation showed that regardless of the type of VHC, the cost of one inhalation procedure with the use of pMDI was 1.6–2.4 times lower compared to NEB and amounted to PLN 9.39. The most expensive method of SABA administration for the payer was NEB using a constant-output jet nebulizer (PLN 22.84) (Tables 4 and 5).

Discussion

Short-acting β_2-agonists and their combinations with short-acting muscarinic antagonists (SAMA) are, next to corticosteroids (ICS), the most commonly used inhaled drugs in children [1, 2, 19–21]. They are used in the therapy of various diseases, although for many years they have been mainly used in the treatment of asthma [1–3]. According to the recommendations of GINA and the Polish Inhalation Guide, these drugs should be used when necessary in the event of an exacerbation of the disease and administered using pMDI + VHC or alternatively in NEB in both outpatient and hospital treatment [1, 2, 5, 22].

Polish research results indicate that hospital treatment of asthma exacerbation in adults is 7.6 times more expensive than outpatient treatment. Moreover, it has been shown that the cost of pharmacotherapy constitutes only 20% of the direct costs associated with hospital treatment [23]. It is important to look for diagnostic and therapeutic methods that, with high efficiency, will enable the reduction of hospital treatment costs. A cost analysis was carried out for inhalation pharmacotherapy of airway obstruction in children with asthma exacerbation conducted in the non-invasive treatment ward of one of the university children's hospitals in Poland. For the administration of inhalation drugs, dual-valve, small-volume and low-resistance VHC are used, as well as nebulizers with high clinical efficiency (a constant-output jet nebulizer with mass median aerodynamic diameter (MMAD) regulation function, and an active mesh nebulizer). There are many VHCs available on the Polish market with various parameters, applications and prices. However, only a few meet the criteria of a modern VHC recommended by experts for children. One of them is AeroChamber Plus Flow-Vu® – the most thoroughly tested in vitro and in vivo VHC, and the most commonly used one in the world [4, 5, 24].

The development of technology enabling the precise dosing of inhaled drugs has contributed to the increasingly frequent selection of NEB as aerosol therapy methods. This applies especially to newborns and infants. The role of mesh nebulizers, which generate homogeneous aerosol particles (monodisperse aerosol) and are characterized by low drug losses, short nebulization time and high predicted lung deposition, is becoming increasingly important [25–27].

Pollock *et al.*'s summary of the systematic reviews to date of the use of bronchodilators in children with asth-

ma exacerbation clearly indicates that SABA are the safest and have the greatest clinical efficacy among inhaled anti-obstructive drugs. Application by patients of SABA with the use of pMDI + VHC compared to NEB reduces the need for hospitalization of a child with bronchial obstruction < 3 years of age by 44%, while in older children it shortens the duration of stay in the emergency department by about 30 min [3].

Research results also indicate that regardless of the method of calculation, the use of SABA with pMDI + VHC instead of NEB ensures a reduction in total costs both in the emergency department and the hospital ward. The cost of one inhalation procedure using pMDI + VHC was 18–63% lower compared to the cost of NEB. Differences in expenditure were observed in all children with bronchial obstruction regardless of their age. The lower cost of SABA supply with the use of pMDI + VHC compared to NEB resulted mainly from: (i) shorter inhalation time (3 min for pMDI + VHC vs. 20 min for NEB), and thus a lower cost of the nurse's work, (ii) greater clinical effectiveness of SABA administered via pMDI + VHC vs. NEB, which translates into a smaller number of additional procedures performed in the emergency department, shorter time of the child's stay in the emergency department and lower risk of hospitalization, (iii) higher efficiency of SABA packaging with pMDI vs. solution for NEB, and (iv) lower cost of additional materials (disinfectant liquid, gloves, syringes) needed for administering the drug via pMDI + VHC vs. NEB [10–15].

Our analysis has similar results. From the payer's perspective, the cheapest was inhalation using SABA with pMDI + VHC. It was also observed that regardless of the type of VHC and type of the anti-obstructive drug, the cost of one inhalation procedure using pMDI was 1.5–2.4 times lower compared to NEB.

The differences in expenses were related to the prices of drugs, devices for their administration, costs of sterilization, and the working time of medical staff. The cost of drugs in pMDI per inhalation procedure was almost 9 times (SABA) or 3 times (SABA + SAMA) lower than the cost of the same drugs for NEB. Israeli researchers have provided identical observations. Breuer *et al.* indicated that the estimated annual cost of SABA consumption in a solution for NEB in the paediatric ward of a university hospital was 2.5 times higher than the cost of SABA administration via pMDI + VHC [14].

The cost of the inhalation procedure is also significantly affected by the possibility of using one device for administering drugs to different patients. While in the case of nebulizers this is widely used, VHC in some of the analysed studies were dedicated to one patient [10, 11]. Salyer *et al.* have shown that the use of a new VHC in each patient resulted in more than a twofold increase in the cost of inhalation using pMDI [11]. In our hospital, VHC, similarly to nebulizers, undergo a gas sterilization process (ethylene oxide), which significantly reduces their operating costs [28]. However, the cost of using VHC per inhalation procedure is still higher than the cost of using a nebulizer once (PLN 0.61 vs. PLN 0.13–0.15). Moreover, the costs of purchasing and using a VHC are about 30% higher when the drug is administered through a mask.

Researchers also note that the duration of drug administration has the greatest impact on the total cost of the inhalation procedure. Salyer *et al*. indicated that the time needed to prepare and administer the drug by pMDI + VHC was estimated at 13.2 min, while in NEB at 20.4 min [11]. In turn, in the work of Mason *et al.*, whose data were used in our analysis, the administration of the drug via pMDI took less time (2–3 min) and the duration of NEB was estimated at 20 min [18]. The duration of inhalation procedure determines the expenses related to the work of the medical personnel involved in this procedure. Usually the person performing the inhalation procedure is a nurse. Her employment costs vary from one country to another. However, in each analysis, the estimated cost of a nurse's work was significantly higher during NEB vs. drug supply with the use of pMDI + VHC. In the study by Breuer *et al.* the estimated cost of a nurse's work on administering inhalation drugs to 250 patients with asthma exacerbation was calculated at $1,481 when pMDI + VHC was used and $7,407 when the doctor recommended NEB [14]. According to our calculations, a nurse costs a payer 2.3 to 6.6 times more when a child receives anti-obstructive drugs in NEB. In the USA, 3-year observations have shown that shortening the time of SABA administration by replacing NEB with drug supply via pMDI + VHC is associated with a reduction in total costs by up to 21% [11]. In Staggs *et al.* study it was shown that replacing SABA supply in NEB with pMDI + VHC shortened the child's stay in the emergency department by over 30 min (faster relief of asthma exacerbation, reduction in the number of procedures performed), which resulted in savings of $213,532 per year [12].

The analysis also showed differences in the scope of direct NEB costs depending on the type of the nebulizer used. It has been estimated that the real cost of NEB using a mesh nebulizer is 1.5 times lower vs. NEB using a constant-output jet nebulizer (Tables 4 and 5). These differences result from: (i) shorter working time of medical staff when performing NEB with a mesh nebulizer vs. a jet nebulizer (7 min vs. 20 min), (ii) 7 times smaller RV of the mesh nebulizer (0.1 ml vs. 0.7 ml), which translates into a lower cost of the drug needed to fill this space, (iii) lower cost of sterilizing the mesh nebulizer vs. jet nebulizer (smaller dimensions of the elements of the mesh nebulizer, which are gas sterilized).

In the University Children's Hospital in Lublin, inhalation procedures using SABA or SABA + SAMA are performed in 5 wards (neonate pathology ward, infant pathology ward, pulmonology, allergology, and intensive care unit). Assuming that about 6000 inhalation proce-

dures are performed per year using pMDI + VHC with a mouthpiece instead of NEB, the estimated annual hospital savings would be approximately PLN 28,000-81,000.

Conclusions

In hospital treatment of asthma exacerbations, the direct cost of SABA or SABA + SAMA inhalation by pMDI + VHC is lower compared to the cost of NEB. The direct cost of SABA or SABA + SAMA nebulization when using a mesh nebulizer is lower compared to the cost of NEB of the same drugs carried out with a constant-output jet nebulizer. The actual cost of the inhalation procedure consists of direct medical costs (prices of drugs, devices for their administration, remuneration for medical staff) as well as direct non-medical costs (cost of personal protective equipment, sterilization of drug delivery devices). The working time of medical staff during the inhalation procedure is the component generating the highest cost for the hospital.

Conflict of interest

The authors declare no conflict of interest.

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