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MINIREVIEWS

Drug delivery interfaces: A way to optimize inhalation therapy in spontaneously breathing children

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Abstract

There are several different types of drug delivery interfaces available on the market. Using the right interface for aerosol drug delivery to children is essential for effective inhalation therapy. However, clinicians usually focus on selecting the right drug-device combination and often overlook the importance of interface selection that lead to suboptimal drug delivery and therapeutic response in neonates and pediatrics. Therefore, it is necessary to critically assess each interface and understand its advantage and disadvantages in aerosol drug delivery to this patient population. The purpose of this paper is to provide a critical assessment of drug delivery interfaces used for the treatment of children with pulmonary diseases by emphasizing advantages and problems associated with their use during inhalation therapy.

Key words: Aerosols; Inhalation therapy; Children; Masks; Mouthpiece; High flow nasal cannula; Blow-by; Hood; Spacer/valved holding chamber

Core tip: Many interfaces exist for aerosol drug delivery to spontaneously breathing children and inhalation therapy with different interfaces has become an important topic of interest among clinicians. However, clinicians usually focus on selecting the right drug-device combination and often overlook the importance of interface selection that lead to suboptimal drug delivery and therapeutic response in neonates and pediatrics. This paper provides a critical assessment of drug delivery interfaces used for the treatment of children with pulmonary diseases by emphasizing advantages and problems associated with their use during inhalation therapy.

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INTRODUCTION

There are several different types of drug delivery interfaces available on the market. Using the right interface for aerosol drug delivery to children is essential for effective inhalation therapy. However, clinicians usually focused on selecting the right drug-device combination and often overlooked the importance of interface selection that lead to suboptimal drug delivery and therapeutic response in neonates and pediatrics[1-6]. Therefore, it is necessary to critically assess each interface and understand its advantage and disadvantages in aerosol drug delivery to neonates and pediatrics. The purpose of this paper is to provide a critical assessment of drug delivery interfaces used for the treatment of children with pulmonary diseases by emphasizing advantages and problems associated with their use during inhalation therapy.

BLOW-BY

Blow-by is a technique that is used with a jet nebulizer placed within a distance from the child and directs aerosol plume towards the patient's face. Historically, aerosolized medications were delivered to neonates and pediatrics using blow-by because it was considered to be an effective technique especially for crying, fussing and uncooperative children. Also, many parents preferred to use blow-by, a mask-free aerosol delivery technique, to avoid struggling with their children during inhalation therapy.

However, there are several disadvantages of this technique. For instance, it cannot be used with pressurized metered-dose inhalers (pMDIs) with valved holding chambers (VHCs) and breath-actuated nebulizers due to poor mask seal that will inhibit valve opening[7]. Also, blow-by cannot be used with mesh nebulizers due to lack of supplemental gas flow[7]. Previous research reported that blow-by is not efficient in aerosol drug delivery to children because it results in 50%-85% lower dose than the facemask[8-11]. Therefore, using blow-by for aerosol therapy is not recommended[7,11-13].

Problems associated with blow-by highlight not only the importance of interface selection in inhalation therapy, but also finding a better alternative for delivering aerosolized medications to neonates and pediatrics. Mouthpiece, facemask, nasal mask, pasifier mask, hood, high flow nasal cannula and VHCs may be viable choices of interface in children and the following sections will describe each interface more in detail.

MOUTHPIECE

Previous *in vitro* studies showed that aerosol delivery *via* a mouthpiece may provide twice as much drug compared with a facemask and is the most effective interface in spontaneously breathing older pediatrics[14,15]. Since children less than 3 years of age cannot keep the mouthpiece in their mouth with an adequate seal during inhalation therapy, the mouthpiece is not the right interface for them[16-19]. Therefore, when a mouthpiece cannot be used by a child, choosing another interface such as facemask, high flow nasal cannula or hood is important to improve the efficiency and efficacy of aerosol drug delivery to neonates and pediatrics.

FACEMASK

Facemasks are commonly used for aerosol drug delivery to children until they develop sufficient understanding to inhale through the mouthpiece during inhalation therapy. In children who cannot use a mouthpiece until 3 years of age, clinicians should consider using a well-fitting facemask. Therefore, it is essential to select a lightweight and flexible facemask with anatomic contours and small dead space in order to increase tolerability of facemask by children during inhalation therapy[20,21]. Using smaller masks with less dead space in neonates will lead to a greater inhaled dose especially with use of aerosol devices such as mesh nebulizers or pMDIs that do not add gas to the system during treatment.

Facemasks designs can be divided into two categories: (1) front-loaded facemasks and (2) bottom-loaded facemasks. Front-loaded facemasks have small entrainment ports on the side of the mask and direct aerosol toward the oronasal area of the patient as opposed to bottom-loaded masks that direct aerosol toward the upper part of the mask. Previous research reported that aerosol deposition with the front-loaded facemask (Bubbles Fish Ⅱ Mask, PARI, Midlothian, Virginia) was greater than bottom-loaded facemask[8,22-24]. They also have lower deposition in the eye and face compared with bottom-loaded facemask designs[22,23,25].

When a facemask is used for aerosol drug delivery to neonates or pediatrics, clinicians should have a good face-mask seal to maximize the efficiency of treatment and prevent the drug from getting to the eyes and the face of children. However, keeping a good face-mask seal during inhalation therapy is frequently associated with crying and rejection of the facemask. Previous research showed that aerosol drug delivery to children will decrease significantly without an optimum face-mask seal because of leaks, crying or children intolerance of the facemask[2-4,22,25-29]. Janssens *et al*[30] suggested that administration of inhaled medications while children are asleep may be a viable option for inhalation therapy because children have more regular breathing patterns during sleep that may lead to greater lung deposition and better patient outcomes. However, Esposito-Festen *et al*[31] reported that 69% of the young children woke up and 75% of them distressed during inhalation therapy with the pMDI and VHC combination.

In the past, clinicians believed that crying improves aerosol drug delivery to children because of the large breath at the end of the cry. However, crying results in a

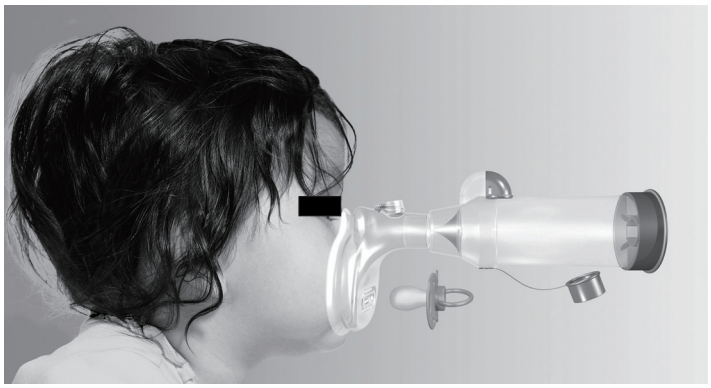

Figure 1 Soother mask (Reproduced with permission from the InspiRx, Somerset, New Jersey).

very long exhalation followed by fast and short inhalation that leads to deposition of aerosolized medications in the upper respiratory track than in the lower respiratory therapy track. Also, it is difficult to have a good seal with the facemask when a baby cries. Using a facemask with the pMDI - VHC, Tal *et al*[32] found that lung deposition of babies crying was 0.35% as opposed to 2% when they have quite breating. Similarly, Murakami *et al*[33] showed that aerosol deposition in a crying infant using a facemask with a nebulizer was negligible and Iles *et al*[34] reported a 4-fold decrease in lung deposition when infants were crying. According to the findings of the study conducted by Wildhaber *et al*[35] the gastrointestinal deposition in crying children was 50% higher than their non-crying peers.

PACIFIER MASK

As a new and innovative development of chidren-oriented drug delivery interface, the pacifier mask (Soother Mask, InspiRx, Somerset, New Jersey) was designed to achieve therapeutic lung deposition in children by eliminating their discomfort, fear and cry with the conventional facemask and keeping them calm through a pacifier. It includes the infant's own pacifier that is attached to the anterior wall of the mask (Figure 1). The infant keeps the Soother mask sealed to his face by sucking the pacifier during treatment while nasally inhaling aerosolized medications generated by pMDIs/VHCs or nebulizers during inhalation therapy[36,37]. Amirav *et al*[38] compared the Soother mask with a conventional bottom-loaded face mask on bronchodilator delivery in 12 infants less than 1 year of age. Using scintigraphic measurements of aerosol deposition in infants, they reported that lung deposition with the Soother Mask was similar to that with the conventional face mask without a pacifier[38]. Since sucking calms children, the Shooter Mask can be used for prolonged periods of time without rejection by infants and improves compliance to aerosol treatments in infants[18,36-38].

HIGH FLOW NASAL CANNULA

Infants and young children are nose breathers. Since previous research showed that nasal delivery of aerosolized medications to the lungs of infants and pediatrics is superior or more effective than oral delivery[39,40], aerosol delivery through high flow nasal cannula (HFNC) has become a popular procedure in the treatment of children with pulmonary diseases. Several *in vitro* studies evaluated aerosol drug delivery through HFNC in infants and pediatrics[41-44]. Using dose quantification with the laser diffraction technique, Bhashyam *et al*[43] determined the efficiency of inhalation therapy through adult and pediatric HFNC with a mesh nebulizer placed downstream of a heated humidifier. They reported that aerosolized medications could be efficiently delivered to pediatrics through HFNC. Ari *et al*[44] compared aerosol drug delivery with helium-oxygen mixture (heliox) and oxygen at 3 L/min and 6 L/min, using a pediatric HFNC with a mesh nebulizer placed on the inspiratory inlet of a heated humidification system. They reported that bronchodilator delivery with heliox at 3 L/min was similar to that with oxygen whereas heliox delivered 2 fold greater aerosol than oxygen at 6 L/min. Sunbul *et al*[42] evaluated bronchodilator delivery using HFNC, bubble continuous positive airway pressure (CPAP) and sigh intermittent mandatory ventilation (SiPAP) with a mesh nebulizer placed proximal to the patient interface and prior to the humidifier. Using spontaneously breathing lung model attached to a low-birth-weight anatomic nasal airway cast, they showed that aerosol delivery with SiPAP was lower than HFNC and the Bubble CPAP. Aerosol deposition through HFNC was less than 2% but higher than drug delivery with the Bubble CPAP. Also, nebulizer placement at the humidifier resulted in greater aerosol deposition in HFNC, SiPAP and Bubble CPAP[42]. According to Perry *et al*[41] HFNC should not be used for bronchodilator delivery to children because the amount of aerosol deposition obtained with different cannula sizes of flows used with HFNC was lower than the amount needed for a clinical response. Also, skin irritation and condensate accumulating in the cannula are potential issues with HFNC. Therefore, clinical studies evaluating the safety and efficacy of aerosol drug delivery with HFNC are warranted.

NASAL MASK

Nasal masks were developed in recent years to improve

Table 1 Descriptions, advantages and disadvantages of each interface used for aerosol drug delivery to spontaneously breathing neonates and pediatrics

Interface	Description	Advantages	Disadvantages	Suggestions for the best practice
Blow-by	A technique that directs aerosol plume towards the patient's face by placing a jet nebulizer within a distance from the child that ranges from 1 to 30 cm	Easy to use Comfortable and easy to tolerate by the patient A mask-free aerosol delivery technique Used with fussing, crying and uncooperative children	Inefficient aerosol drug delivery to children Drug delivery with blow-by is 50%-85% less than the facemask Cannot be used with pMDIs, breath- actuated nebulizers and mesh nebulizers	Inhalation therapy with blow-by is not efficient; therefore, it should not be used for aerosol drug delivery to neonates and pediatrics
Mouthpiece	A cylindrical tube that extends between the lips so that aerosol can pass through the oropharynx to reach lower respiratory tract	Efficient inhalation therapy in children Aerosol drug delivery with a mouthpiece is two-fold more than that with a face mask	Children less than 3 yr of age cannot use a mouthpiece An adequate consistent seal is needed during inhalation therapy	The mouthpiece should not be used for children who are less than 3 yr old When using a mouthpiece child should be encouraged to keep it in their mouth during therapy If a child cannot keep the mouthpiece in his mouth with an adequate seal during aerosol drug delivery, another interface should be used for inhalation therapy
Facemask	An interface that covers the nose and mouth. It is kept in place through an elastic band that extends beyond the back of the head or neck	Can be used in children all years of age Can be used with nebulizers and pMDIs to deliver aerosolized medications to neonates and pediatrics	A good facemask seal is needed for optimum aerosol drug delivery Is frequently associated with crying, intolerance and rejection of the mask Crying and leaks between face and mask decrease aerosol drug delivery to children	Select a lightweight and flexible facemask with anatomic contours to increase tolerability of face mask by children during therapy Choose a facemask with small dead space and have a good face-mask seal to increase delivery efficiency of inhalation therapy Use another interface if the patient starts to fuss, and cry during aerosol drug delivery with a facemask
Pacifier mask	A face mask with the attachment of the infant's own pacifier	A new and innovative facemask design that eliminates fear, discomfort and cry with the standard facemask A children-oriented drug delivery interface designed to achieve therapeutic lung deposition in children Improves compliance to inhalation therapy in infants		May be a good option for children who fuss, cry and does not tolerate other interfaces used for aerosol drug delivery in neonates and pediatrics
Nasal mask	An interface that covers the nose to allow aerosol to pass through the nasopharynx to reach the lower respiratory tract	Easy to use Better tolerance than the facemask	Aerosol delivery with the nasal mask is less than that with the standard facemask	
High flow nasal cannula	A tubing with two small prongs that are inserted into the nares to allow aerosol pass through the nasopharynx and reach the lower respiratory tract	Efficient delivery of aerosolized medications to neonates and pediatrics Children may tolerate HFNC better than the facemask	More information about the safety and efficacy of aerosol drug delivery though HFNC is needed Cannot be used with pMDIs	When using mesh nebulizers for aerosol drug delivery to neonates and pediatrics, place the nebulizer prior to the heated humidifier
Hood	An enclosure that covers the head and neck of a neonate or small children to deliver aerosol to the lungs while isolating it from ambient air	A good option for aerosol delivery to children who cannot use a mouthpiece and tolerate the facemask Likelihood of agitating infants and making them cry is low Aerosol delivery with the hood is the same as the facemask Parents prefer the hood over the mask	User may need additional training and practice to provide proper inhalation therapy with the hood More time and parts may be needed for the set-up	Use the hood for aerosol drug delivery to children who cannot use a mouthpiece and tolerate the facemask Put the infant in the face-side position when using the hood for inhalation therapy because it has less facial-ocular deposition than face-up position

Valved holding chamber	A chamber shaped interface with a one-way valve that allows aerosols to be contained in the chamber during aerosol therapy	Reduces oropharyngeal deposition Minimize hand-breath coordination during inhalation therapy Improves efficiency of aerosol therapy	Electrostatic charge and large volume VHCs result in a decrease in aerosol drug delivery to children	Wash the VHC with detergent and air dry before inhalation therapy in order to eliminate static charge and improve aerosol delivery to neonates and pediatrics Choose small volume VHCs for aerosol therapy Actuate one-dose at a time into VHC instead of multiple doses

VHC: Valved holding chambers; pMDIs: Pressurized metered-dose inhalers.

aerosol drug delivery to neonates and pediatrics. The nasal mask is a special type of mask that is placed over the nasal airway during inhalation therapy. A recent *in vitro* study showed that aerosol delivery with the nasal mask was less than that with the facemask in simulated spontaneously breathing infants and young children using a jet nebulizer[24].

HOOD

Hood is a good option for aerosol drug delivery to children who cannot use a mouthpiece and tolerate the facemask[18,45-48]. Since there is no attachment to the patient's face, the likelihood of agitating infants and making them cry with the use of hood for inhalation therapy may be less than facemasks. Aerosol drug delivery *via* hood is easy to operate and often provided when infants are asleep. Amirav *et al*[49] showed that bronchodilator delivery with the hood and facemask was similar (2.6% and 2.4%, respectively) in 14 wheezing children. Kugelman *et al*[47] reported that both treatment time and discomfort were lower in infants using the hood. In another study, Amirav *et al*[48] found that respiratory scores of infants with bronchiolitis received aerosol therapy with the hood and facemask were similar, but parents preferred the hood over the masks[48]. It is also important to ensure the optimal position of the child within the hood. Kim *et al*[50] found similar lung deposition in face-up and face down positions during hood nebulization; however, the face-side position has less facial-ocular deposition than face-up position.

VALVED-HOLDING CHAMBERS

VHCs are commonly used with pMDIs in order to decrease oropharyngeal deposition and minimize hand-breath coordination in children[12,51]. According to previous research, spacers and VHCs should be washed with detergent and air-dry to eliminate static charge and improve aerosol delivery to infants and pediatrics[52-55]. Thus, deposition of drug particles on the inner surface of the spacer or VHC will be eliminated. Another alternative would be to use anti-static spacers/VHCs during inhalation therapy in children[56].

Also, infants and toddlers may not empty aerosolized medication from a large volume spacer of 200-700 mL. Therefore, it is important to use small volume spacers or VHCs so that the concentration of aerosol in the VHC is kept higher and children can inhale all the medication in less time with fewer breaths. Parents need to be educated to actuate one dose at a time into VHC instead of multiple doses and let their children inhale from VHC right after the pMDI has been actuated[12,57].

EDUCATING PARENTS ABOUT INTERFACES USED IN INHALATION THERAPY

Typically, inhaled medications are prescribed without demonstrating parents how inhalation therapy should be undertaken with each device and interface. Therefore, parents don't know how to use each interface and how to solve problems that may arise during aerosol drug delivery to children. For instance, when their baby fights with the facemask, some parents may decide to use blow-by without knowing that it will reduce the efficiency of therapy and others force the baby to accept the facemask by holding it tightly on the baby' s face and believing that crying improves aerosol drug delivery to their children. As a result, parents report poor response to inhalation therapy to their physicians who usually decide to increase the dose or change the inhaled agent as they assume parents' technique in aerosol drug delivery is adequate[18]. Therefore, parental awareness and training on proper technique with each interface during inhalation therapy is essential. Table 1 includes descriptions, advantages and disadvantages of each interface used for aerosol drug delivery to spontaneously breathing neonates and pediatrics. After careful instructions on how to use and handle an aerosol device, clinicians should reinforce instructions on a regular basis and the choice of drug delivery interface should be re-assessed[58].

In conclusion, delivering aerosolized drugs through different interfaces to children poses a number of challenges. Clearly, there is a need to develop more acceptable and child-friendly interfaces in order to improve aerosol drug delivery to this patient population. New interfaces should take into account the special needs and respiratory characteristics of children. Meanwhile, educating parents and healthcare professionals about drug delivery interfaces used in inhalation therapy is

essential for the well-being of neonates and pediatrics.

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