Role of Nebulized Hypertonic Saline in Pediatric Patients with Bronchiolitis

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Abstract

Background: Bronchiolitis is an acute inflammatory injury of the bronchioles. It is one of the most common lower respiratory tract infections (LRTI). It is seasonal infection, beginning in late October, peaking in January or February, and ending in April. Internationally, independent of region, respiratory syncytial virus infection peaks consistently during annual or biannual epidemics. Hypertonic saline inhalation therapy has been studied in numerous clinical trials with mixed results. Since the pathology of bronchiolitis involves airway inflammation and mucus plugging, improving mucus clearance should be beneficial in resolving bronchiolitis. Hypertonic saline shifts the flow of water into the mucus layer by osmosis, reducing submucosal edema, reducing viscosity of mucus, improving mucus clearance, and rehydrating the airway surface liquid. The updated AAP (American Academy of Pediatrics) guidelines 2014 support the use of hypertonic saline nebulization for infants and children hospitalized for bronchiolitis.

Background
Bronchiolitis
Bronchiolitis is mostly viral in origin and respiratory syncytial virus (RSV) is the most common causative virus. Other less common viruses include influenza A and B, parainfluenza viruses, adenovirus, rhinovirus, Mycoplasma pneumonia and Human metapneumovirus (HMPV) (1).

In 2014, the American Academy of Pediatrics (AAP) guidelines defined bronchiolitis as a viral upper respiratory infection prodrome followed by wheezing and respiratory effort in children younger than 2 years old (2).

Epidemiology
Bronchiolitis is a seasonal infection, beginning in late October, peaking in January or February, and ending in April. Internationally, independent of region, respiratory syncytial virus infection peaks consistently during annual or biannual epidemics. Although the peak and duration of these epidemics vary worldwide, they are steady year-to-year within a country. Indoor crowding in population-dense areas during cooler months or rainy seasons might be one factor that facilitates viral transmission. Additionally, weather-related factors, such as cold and dry air inhalation that might ruin ciliary function, the airway mucosa, and inhibition of temperature-dependent antiviral responses, might influence both disease transmission and severity. Environmental tobacco smoke has been associated with increased risk for respiratory syncytial virus-attributable admission to hospital and disease severity as well. As with other respiratory viral infections, the risk of severe respiratory syncytial virus bronchiolitis might be greater in boys than in girls. This variance might be due to differences in lung and airway maturation, and by genetic aspects (3).

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In Egypt RSV is listed as an important viral cause of severe LRTI requiring PICU admission in children younger than two years old. An age distribution analysis showed RSV infections occurred in significantly younger patients with peak during the month of January and February (8).

Bronchiolitis is an acute infectious disease of the lower respiratory tract that occurs primarily in young infants, most often in those aged 2-24 months. Seventy-five (75%) percent of cases of bronchiolitis occur in children younger than 1 year, and 95% in children younger than 2 years. Incidence peaks in those aged 2-8 months. Annual incidence is 11.4% in infants younger than 1 year and 6% in those aged 1-2 years. Prevalence may be higher in urban areas (9).

**Nebulized hypertonic saline (3%)**

It is an increasingly planned therapy for acute viral bronchiolitis. It should be considered a safe and an effective treatment for infants with viral bronchiolitis. Even in mildly affected young children, it is mostly faster and more convenient to use a relatively small amount of hypertonic saline. Physiological evidences suggest that the use of nebulized hypertonic saline increases the mucociliary clearance in normal or affected lungs. Because the pathology in bronchiolitis involves inflammation of the airways and subsequent mucus plugging, improving mucociliary clearance would be very beneficial. A more particular theoretical mechanism of action has been based on the concept of the rehydration of airway surface liquid (5).

**The Egyptian Bronchiolitis Guideline Adaptation Group in 2019**, recommends that clinicians may administer nebulized hyper tonic saline to infants and children hospitalized for bronchiolitis according to the [American academy of Pediatrics guideline 2014-2018](Evidence: B Moderate recommendation).

**Table 1: Summary of Clinical Trials for HYPERTONIC SALINE in Bronchiolitis treatment** (6)
Rationale of hypertonic saline (HS) aerosol in treatment of bronchiolitis

The main mechanism of action of nebulized hypertonic saline is through modulation of airway surface liquid (9).

Physiology of the Airway Surface Liquid (ASL)

As described in the figure below the large airways as trachea and bronchi, contain numerous sub-mucosal glands which are lined by ciliated pseudostratified columnar epithelial cells with relatively few goblet and brush cells. The epithelium in bronchioles is more columnar, with Clara cells scattered among the ciliated cells. Light and electron microscopy define two ASL layers: the periciliary liquid or sol layer, adjacent to the airway epithelium covering the cilia, and the overlying viscous gel layer. The cilia are bathed in the periciliary liquid, whose pH, ionic composition, and physical properties are believed to have an important role in mucociliary clearance. The ASL is an aqueous solution containing ions, glycoproteins including mucins, and other proteins such as lactoferrin, IgA, defensins, lysozyme and antimicrobial surfactant proteins (7).

The ASL is thought to have an important role in airway hydration, innate immunity, and antimicrobial defense mechanism. In principle, the ASL could vary in osmolality between hypo-osmolar, iso-osmolar, or hyperosmolar (compared with blood osmolality) depending on the relative impact of epithelia transport, surface tension effects, and convective/evaporative fluid losses (7).

Figure (1): Schematic of ASL in large and small airways, showing gel and periciliary liquid layers.
Possible mechanisms of airway surface liquid (ASL) dehydration in viral bronchiolitis (5).

Efficient hydration of airway surface liquid (ASL) necessitates the coordinated interaction between its two layers: mucus layer (ML) and periciliary liquid (PCL).

Figure (2) is a schematic representation of the proposed mechanisms of ASL dehydration in RSV bronchiolitis (Fig. 2 B &C) compared to normal individuals (Fig. 2 A) and CF patients (Fig. 2 D). Since airway epithelia are water permeable, water moves inward following the active absorption of Na through epithelial sodium channel (ENaC) to equalize electrolyte concentrations, thereby causing dehydration of the ASL and outward following Cl transport through both CFTR and Calcium activated chloride channels (CaCC), thus hydrating the ASL. Adenosine stimulates the CFTR, by activating the A28 receptor, to secrete Cl and to weaken ENaC activity, therefore hydrating the ASL (5).

In vivo, ATP activates the P2Y2 receptor thus stimulating CaCC to secrete Cl and directly attenuate ENaC action, thus hydrating the ASL. ATP, which reaches only negligible and ineffective concentrations in static tissue cultures, reaches a higher concentration in vivo (in moving lungs) and is probably the most important hydrating and compensating stimulus for regulating the ASL water content. This increase in ATP concentration, that occurs only in vivo, is due to a mechanism called mechano-transduction in which cells convert a mechanical stimulus into chemical activity. In this case, the phasic motion of the airway flow (lung inflation/deflation and particularly acceleration and deceleration) produces a shear stress, which forces the epithelial cell to release extra-cellular ATP hence hydrating the ASL (Fig. 2 A). This latter mechanism has been revealed to be highly susceptible to viral injury particularly as occurs in RSV infections. Maintaining normal height of the PCL (around 7 mm) is critical for maintaining normal airway mucociliary clearance (MCC) so that the moving tips of the cilia will precisely contact the lower margin of the ML. This is maintained by the ML acting as a water reservoir selectively absorbing water in response to excess hydration and increasing the MCC to super-normal rates (Fig. 2 A). This super-normal MCC was detected in normal personals who inhaled hypertonic saline (HS) aerosols. In contrast, it is suggested that when dehydration of the ASL occurs in response to a relatively mild RSV infection, depletion of extra-cellular ATP concentrations occurs, thus dehydrating the ASL. The (ML) then donates water to preserve at least some MC while maintaining the PCL height close to the normal approximately 7 mm and resulting in ML dehydration (Fig. 2 B). However, when this donor mechanism is exhausted, the ML has no more water to donate, the PCL may start to contract to the point that MCC is impossible (Fig. 2 C). In CF epithelium, which lacks CFTR (Fig. 2 D), is thus absolutely dependent on ATP, the PCL contraction occurs early, even in CF airways exposed to relatively minor viral injury in CF exacerbations (Fig. 2 D). In small babies suffering from severe acute RSV bronchiolitis, the high load of RSV infection in the small sized bronchioles, probably causes a significant reduction of extra cellular ATP that is vital for maintaining ASL hydration in vivo. In addition, the non-specific pathological effect of RSV infection such as the cytotoxic effects on cells, cytokine release and ciliary damage result in mucus plugging of smaller airways (5).
Figure (2) Postulated mechanism in vivo, explaining ASL dehydration in RSV bronchiolitis as compared to normal and CF: (A) normal, (B) mild RSV bronchiolitis; (C) severe RSV bronchiolitis, (D) during viral infection in CF. This figure was modified particularly for RSV bronchiolitis, with the permission and the courtesy of Randell SH and Donaldson SH, both from the University of North Carolina at Chapel Hill (5).

Figure (3): Dehydration of the ASL occurs in response to RSV infection, extra-cellular ATP concentrations are depleted, thus dehydrating the ASL (5).
Rationale of Hypertonic Saline Aerosol Treatment in RSV Bronchiolitis

Infants with acute viral bronchiolitis wheeze but as the pathophysiology of bronchiolitis is pretty distinct from that of asthma, these infants are less if at all responsive to bronchodilators or steroids. Bronchiolitis is a viral infection of the bronchial and bronchiolar epithelium, with subsequent per bronchiolar mononuclear infiltration and epithelial cell necrosis, profound sub-mucosal edema, increased mucus secretions and therefore an increase in mucin/water ratio that causes relative dehydration of air surface liquid (ASL). Moreover, RSV decreases extra cellular ATP by increasing ATPase levels and therefore results in loss of ENaC (Epithelial sodium channel) inhibition (increasing Na absorption) and loss of the attenuation of outward secretion of chloride. Thus, more water will move along with these electrolytes from the ASL to the sub-mucosa. This will result in more dehydration of the ASL, and decrease in the height of the mucus layer. Thus, hypothetically, in more severely affected bronchiolar areas; the airway surface liquid protective hydrating mechanism can be injured thus depleting not only the mucus layer’s water content but also damaging the ASL, and epithelial architecture while the depleted height of the periciliary liquid (PCL) impairs mucus clearance (MC) (5,10).

Therefore, appropriate treatment strategy necessitates hydration of the airway surface liquid, decrease the sub mucosal edema and improve the mucus rheological properties (elasticity and viscosity) and thus improve mucous clearance. Nebulized hypertonic saline may, in theory, reverse some of these pathophysiological abnormalities in acute viral bronchiolitis. In vitro, the addition of hypertonic saline increases airway surface thickness, improves mucus rheological properties (elasticity and viscosity), decreases epithelial edema and accelerates mucus clearance rates. In vivo, hypertonic saline inhalation increases the rate of mucociliary transport even in normal subjects with no proven evidence of dehydration, mucus hyper-secretion or sub-epithelial edema (5, 11).

Additional Important Modes of Action of Aerosolized Hypertonic Saline in Treatment of Bronchiolitis

Even though hydration of the ASL is considered the main mode of action, additional important mechanisms are attributed to the effect of HS by which HS improves MC by ciliary action or cough reflex. Hypertonic saline breaks the ionic bonds within the mucus gel. This, in turn, reduces the degree of cross-linking and entanglements, and so improve mucus rheology. HS increases frequency of ciliary beats via the release of prostaglandin E2 (PGE2). Addition of hypertonic saline raises the ionic concentration in the mucus and brings about a conformational change by “shielding” the negative charges, thereby reducing repulsion. These leads to a more compact mucus macromolecule, and more effective cough-dependent MC. Airway surface liquid hyperosmolarity can release mediators capable of enhancing ciliary activity. Moreover, by absorbing water from the mucosa and sub-mucosa, hypertonic saline solution can theoretically reduce edema of the airway wall in infants with acute bronchiolitis. Hypertonic saline inhalation can also cause cough and sputum induction, which can help in the sputum clearance from the airways and thus enhancing the edema obstructing the airways (12,13).
Figure (4): Simplified scheme assuming only osmotic forces to control water transport (5).

References

