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Review Article

Effect of Epinephrine Nebulization in the Management of Acute Bronchiolitis

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Abstract:

Acute bronchiolitis is infection of bronchioles that affect infant and it consider as one of the major cause of hospital admissions. In this review we described the effect of nebulize epinephrine in acute bronchiolitis treatment. Epinephrine's vasoconstrictive and bronchodilator properties make it a promising intervention, especially in reducing airway edema and improving clinical outcomes. But its short acting and the use still controversial.

An awareness of the effect of using nebulized epinephrine helps health worker to manage the disease and reduce morbidity and hospitalization.

Key words: acute bronchiolitis; nebulized epinephrine; adrenaline

Introduction

Bronchiolitis, an inflammation of the bronchioles, is the predominant viral respiratory system infection among babies and toddlers under two. Each winter, numerous pediatric emergencies arise because of breathing difficulties along with inadequate feeding accompanied by these viral infections. Physicians face the dual challenge of alleviating obstructive symptoms during acute episodes and preventing recurring airway obstruction symptoms that can persist for years following the initial bronchiolitis episode. In Great America, more than 125,000 infants face hospitalization annually due to this condition [1]. The viruses responsible for bronchiolitis encompass a range of pathogens, such as rhinovirus (RV), adenovirus, and parainfluenza virus. We will not forget the respiratory syncytial virus (RSV), which is considered a supposed danger to the respiratory health of children, especially young infants. It also poses risks to children with congenital conditions such as bronchopulmonary dysplasia (BPD) and congenital heart defects (CHD) [2], [3].

The typical pathophysiological changes associated with this inflammation primarily affect the terminal bronchioles, leading to swelling, loss of healthy epithelial cells, exudate production with secretions, and, consequently, narrowing of airways [4]. Despite these pathological alterations, research indicates bronchodilators can immediately improve clinical assessments. Various treatments have been utilized for this ailment, including β-adrenergic agents such as albuterol and epinephrine and medications that block certain substances in the body known as leukotrienes. The progression of cases during the acute phase and the recovery process has been generally acceptable. However, using nebulized epinephrine remains a topic of debate [5].

This study aims to postulate that epinephrine is a reliable medicine in most moderate and severe airway bronchioles infection cases, potentially offering more advantages than salbutamol in some instances [6]. Its α-adrenergic properties may promote its efficacy on the bronchiolar

mucosa, making it an excellent choice for managing this condition. Some evidence from a single study clarified there was a potential benefit of combining adrenaline and steroids at later time points [7].

Pathophysiology and Clinical Picture:

Bronchiolitis is the predominant viral infection affecting babies and toddlers under two, as they have small, underdeveloped airways that get blocked easily; therefore, they are more likely to develop symptoms. 70% of the conditions are caused by RSV [8,9,10,18]. RSV spreads through the air when someone ill coughs or sneezes or through touching polluted objects. Preventing it can be achieved by avoiding contact with infected individuals and by practicing good hygiene, which includes washing hands often and cleaning surfaces that are frequently touched [11].

Although, the exact pathogenesis is unclear; the virus causes a direct cytotoxic injury to the epithelial lining of bronchioles leading to inflammation and necrosis; subsequently, excessive mucous production and cellular debris accumulation, which obstruct the airways and impede airflow, leading to difficulties with gas exchange, resulting in the symptoms [11,14]. The symptoms are further exacerbated by the immune system's response to the infection; white blood cell accumulation exacerbating the inflammatory process [10].

Bronchiolitis is most prevalent during the winter months and can range from mild to severe, occasionally necessitating hospitalization. Studies found that approximately 30% of admitted patients have combined pathogens, the commonest being RSV alongside human rhinovirus [12].

The Incubation period is approximately 4-6 days. Fever, sneezing, nasal congestion, and rhinorrhea are the initial symptoms, and last from 2 to 4 days, and may be followed by wheezing, cough, labored breathing and feeding difficulties[8]. The signs may include increased respiratory rate, working ala nasi, subcostal, and/or intercostal recession and auscultatory wheezes in addition to crepitations. The condition is usually benign and resolves on its own, and the clinical course is about 10 days [8,9]. Educating the parents about the red flags and alarm signs including, poor feeding, cyanosis and lethargy; which require an assessment by a physician is crucial [9,10]. Estimation of disease's severity is mainly clinical, and the most significant indicator being the impact of the symptoms on the level of consciousness, infant's ability to feed, and the hydration status [8,9,10,11].

Management:

In most of the cases, acute bronchiolitis is benign and resolves on its own [16]. Blood tests and imaging are not routinely recommended, as the diagnosis is mainly clinical [17].

Symptomatic treatment is the base of its management, which involves fluids administration and normal saline nasal drops [12,13,17]. Hospital admission is required if outpatient management failed that means lacking of improvement or worsening symptoms despite treatment at home. Moreover, hospitalization is required if the infant is having symptoms or signs of more severe disease like interrupted feeding, signs of dehydration, poor activity or lethargy, respiratory distress, cyanosis, apnea and if the SPO2 in room air is less than 92% [14,16]. In which cases, oxygenation and bronchodilators might be essential, the use of the latter is controversial and it depends on the clinical judgement of the treating physician [14,17]. Additionally, Infants under the age of three months, premature infants, or those with underlying heart or lung conditions are considered as high risk patients and have a lower threshold for admission [16,17].

Regarding the prevention of bronchiolitis, there is no effective RSV vaccine. However, in infants having critical CHD or BPD, palivizumab is advisable during the first twelve months of life. [11,12,13].

Nebulized epinephrine:

Epinephrine stimulates alpha and beta adrenoceptors. It has been studied for its potential role in treating bronchiolitis symptoms in emergency setting, however; it is not recommended as a routine treatment. It's α adrenergic action can lead to vasoconstriction and airway edema reduction [14,16]. However, the potency of epinephrine nebulization in treating bronchiolitis had been debated [16]. Studies showed mixed results; Some suggest short term improvement, but no significant long term benefits were approved [16].

A study revealed that inhaled adrenaline diluted in thirty percent hypertonic saline markedly minimizes hospitalization period in babies having moderate disease, and ameliorates symptoms acuteness after three days of its administration, however; it doesn't before [22].

Additionally, some studies indicated that nebulized epinephrine, especially when combined with hypertonic saline, may have a modest positive impact on hospitalization period and disease severity in the infants with acute bronchiolitis. Specially it showed a depletion in admission period by approximately 0.35 days and improvement in the clinical condition when evaluated at the second and third day after admission [15].

On other hand, other studies have shown that nebulized epinephrine does not significantly shorten hospital stay or improve respiratory outcome compared to placebo [19,21]. In randomized controlled trial, infants treated with epinephrine did not experience a decrease in the requirements of oxygen or intravenous fluids supplementations, nor did it mark affect respiratory rates or efforts [21].

Salbutamol versus nebulized epinephrine:

An experimental study was directed to investigate the effectiveness of nebulized epinephrine in contrast to Ventolin on hospitalized infants diagnosed with bronchiolitis [25,26]. The findings indicate that in the initial stage of bronchiolitis nebulized epinephrine is more effective than Ventolin and is equally harmless[25,26]. A marked amelioration in the clinical features was noted in infants treated with epinephrine ($P = 0.025$); in contrast to those treated with Ventolin($P = 0.6$). Hence, it was concluded that nebulized epinephrine is more rapid in diminishing he bronchiolitis severity compared to Ventolin ($P = 0.02$) [26].

Additionally, another study was published on 2022 has supported the concept of nebulized epinephrine as an effective agent in bronchiolitis management. This study reinforces that nebulized epinephrine minimizes the financial burden on health organizations [38].

Combination of epinephrine and corticosteroids:

Studies were conducted to investigate the usefulness of combining epinephrine and corticosteroids in the treatment of bronchiolitis and have shown mixed results. Some studies have explored combining the two to maximize bronchodilatation and reduce inflammation [19,20,29], however; the overall outcome was that, the combination had not consistently shown significant benefits over standard supportive care; oxygenation and hydration [30,31], hence; routine use of this combination is not recommended due to deficient proof in improving outcomes [18].

Although, an expremental research was done between 2013 and 2019 on infants diagnosed with severe bronchiolitis and received positive pressure ventilation in ICU. It was concluded that combination of epinephrine and

corticosteroids resulted in reduction of the duration of positive pressure ventilation by 60%(P=,001) [27].

Adverse effects of nebulized epinephrine:

According to the safety profile, epinephrine has minimal side effects, around 1%, most of which are minor and temporary [37].

Suties revealed that using of at least 3 ml of adrenaline (1:1000) leads to a marked tachycardia (151 beats/min) compared with placebo (138 beat/min) (P<0.001) [37].

Additionally, Adrenaline was found to have no statistically significant impact on systemic arterial pressure [37].

Other adverse effects:

Furthermore, randomized controlled trial revealed that 2 doses of 3 ml nebulized adrenaline result in more manifested pallor (P<0.05) compared with Ventolin (P=0.06).

In another study, compared to budesonide, patients who received adrenaline are more presumably to develop side effects, with 17% reporting side effects such as hyper energy, GIT upset, skin rash, and nosebleed [37].

Discussion:

This is a narrative review article to assess The effects of use of epinephrine in management of acute bronchiolitis, which is the most common reason for hospitalization of children in many countries, challenging both economy, area and staffing in pediatric departments, mainly in winter months. [39, 40]

In this articles we review many previous studies, most of studies examining nebulized epinephrine's effectiveness in treating acute moderate bronchiolitis in infants have yielded promising results. When combined with 3% hypertonic saline, this therapy significantly shortens hospital stays and improves clinical outcomes. Notably, clinical benefits emerge after three days of treatment, with extended hospitalizations more likely without epinephrine. [41]. Variations in hospital stay duration across different settings may be attributed to factors such as disease severity, population characteristics and healthcare system differences [42 , 43] .And this findings is also supported by A systematic review and meta-analysis which indicated that nebulized epinephrine ,Especially when combined with hypertonic saline, may have a modest positive impact in the hospitalization days and clinical outcome in the infants with acute bronchiolitis, especially after 72hours after admission [44]. In a comprehensive network meta-analysis, Elliott et al. evaluated the effectiveness of different therapies for treating bronchiolitis. Their findings reveal that nebulized epinephrine, hypertonic saline, and salbutamol significantly reduced admission rates during the critical initial emergency department (ED) visit. Moreover, treatments involving hypertonic saline - whether administered alone or alongside epinephrine - demonstrated a remarkable ability to shorten hospital stays. Despite these benefits, it's important to note that these therapies did not influence the admissions rates within 7 days following the initial presentation. This point highlights the potential for these treatments to improve immediate care outcomes for bronchiolitis [45,46].

In contrast, several studies have demonstrated that nebulized epinephrine does not meaningfully decrease hospital stays or improve respiratory outcomes compared to placebo [41, 47]. For instance, a randomized controlled trial revealed that infants treated with epinephrine did not experience a reduction in the need for supplemental oxygen or intravenous fluids, nor did it notably influence respiratory rates or efforts. This raises important questions about the effectiveness of nebulized epinephrine in treating respiratory distress in infants [47].

Making patients as comfortable as possible is crucial to ensuring the best care during initial treatment. Holding them in a parent's arms or allowing them to sit in a cozy position provides essential comfort. Administer saline nose drops and conduct nasal and oral suctioning to clear the airways effectively. Remember, deep oral and nasal suctioning is not typically necessary. Vigilantly monitor for any apnea signs and prioritize temperature regulation, especially for small infants, to promote their wellbeing and recovery.

Nebulized epinephrine has demonstrated superior effectiveness to salbutamol while maintaining equal safety, as evidenced by a randomized, double-blind trial focused on hospitalized infants with bronchiolitis [48,49]. The findings clearly indicated that infants receiving epinephrine experienced a significant improvement in their clinical scores (P = 0.025), a benefit that was not observed in those treated with salbutamol (P = 0.6). Moreover, treatment with nebulized epinephrine led to a more rapid decrease in the baseline clinical score than salbutamol (P = 0.02). These compelling results underline the vital role of nebulized epinephrine in enhancing the care of bronchial conditions in infants [50].

In use of epinephrine together with corticosteroids in treating acute bronchiolitis studies showed mixed results. The overall outcome was that, the combination had not consistently shown significant benefits over standard. Some studies have explored combining the two to maximize Broncho dilatation and reduce inflammation [51, 52, 53], however the outcome was not consistently shown significant benefits over standard supportive care ; oxygenation and hydration[54, 55].No clear evidence that why most of guidelines suggest not to use this combination routinely. [56]. Although, a randomized controlled trial was performed between July 2013 and November 2019 on infants diagnosed with severe bronchiolitis and received positive pressure ventilation in ICU. It was concluded that combination of epinephrine and corticosteroids resulted in reduction of the duration of positive pressure ventilation by 60%.

Regarding safety profile, research indicates that nebulized epinephrine (1:1000, 3 mL) has a low incidence of adverse events (around 1%).[57]. Many clinical trials revealed that side effect was mild and last temporarily, common side effects include tachycardia, sweating and pallor specially when used after nebulized salbutamol.[58] Serious complications, like arrhythmias, are theoretically possible but rare. Clinical trials show no statistically significant effects on systemic arterial pressure, despite been an adrenergic agent. [59].

Limitations confirmed in this article should be addressed. Firstly, the reliance on aggregated data hinders our ability to evaluate individual patient characteristics and their specific risk factors in the trials. Additionally, one study faced a significant loss in follow-up compared to the control group, which could affect the reliability of the findings. Additionally, many included trials had small sample sizes [60, 61, 62, 63]. Due to the limited number of studies, we could not formally assess publication bias, further underscoring the need for caution in interpreting the results.

This review compellingly highlights significant regional variations in the results across different studies. Notably, research from North America shows more favorable outcomes than studies conducted in the Middle East. This disparity indicates that differences in the standard of care and ethnic backgrounds could impact the results obtained, raising essential questions about equitable healthcare practices.[64]

Our recommendation is to conduct more studies with larger sample size and strict follow up to assess the effectiveness of epinephrine in management of acute bronchiolitis patients.

Conclusion:

This study highlights that using of epinephrine nebulization in acute bronchiolitis remains controversial.

Epinephrine's vasoconstrictive and bronchodilator properties make it a promising intervention, especially in reducing airway edema and improving clinical outcomes. However, its effects are often transient. While some studies suggest it could reduce hospital admissions, the evidence for its long-term benefits is inconsistent.

Additionally, concerns about side effects, like increased heart rate and blood pressure, limit its routine use.

Overall, The use of epinephrine should be evaluated individually, based on the specific circumstances and patient needs, as it may not significantly alter the course of the illness. Although the findings are encouraging, further large-scale studies are necessary to determine its long-term efficacy and safety in routine care.

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