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DO BETA –2 AGONISTS REDUCE ADMISSION RATE IN CHILDREN WITH BRONCHIOLITIS?

***Dr .Mazen Mahmoud*-Pediatrics and Neonatology consultant**
Syrian Board of Pediatrics (SBP)-MSc in pediatric emergency Medicine -University of Edinburgh / UK -Member of the American Academy of Pediatrics (AAP)- Member of RCSEd- The Faculty of Pre-Hospital Care (RCSEd- FPHC)
Email:Drmazenmahmoud@outlook.com
Primary health care corporation -Muaither health center

Abstract

Introduction:

Bronchiolitis is a very common disease in children less than 2 years of age. RSV virus is the major cause of this illness and its admissions represent 18 % of all pediatric hospitalization in infant less than 1 year of age. Globally, RSV infections in children less than 5 years of age account for 3.4 million hospitalizations and the admission rate has relatively increased during the last 15 years, despite the routine use of Beta-2 agonists in children with bronchiolitis in emergency departments.

Methods:

The aim is to determine from the medical literature whether the use of Albuterol in children (less than 2 years of age) with bronchiolitis, reduce admission rate or not?

PubMed, Scopus, web of science and OneFile gale were searched, 1591 articles identified. Randomized controlled trials that comparing Albuterol group recipients with placebo recipients in children (less than 2 years of age) were only included in this study.

Results:

7 (RCT)s representing 670 patients with bronchiolitis published between 1990 to 2011 , Risk of bias generally low and quality of evidence are high, (100%) of included studies have concluded that Beta2 agonists did not reduce Admission rate in children with bronchiolitis (16.5% in Albuterol group vs 20% in placebo group [odd ratio 0.74 , P = 0.20 , confidence interval (CI) = (0.47 - 1.16)].

conclusion:

Use of Beta-2 Agonists in children (less than 2 years of age) with bronchiolitis do not reduce the admission rate.

Key words:

bronchodilator – bronchiolitis - beta 2 Agonist - salbutamol – albuterol Abbreviations:

(RSV) respiratory syncytial virus , (RCT) Randomized controlled trial , (AAP) American Academy of paediatrics

Background and introduction

Bronchiolitis is a widespread illness throughout the world. It commonly affects children particularly patients less than two years of life in the form of epidemics. It is considered as a very common cause of emergency department admissions during the winter season. Bronchiolitis is characterized by high morbidity and low mortality, almost 1 in 3 infants will suffer from signs and symptoms of bronchiolitis during the first year of infant life. However, death because of severe respiratory distress is generally rare and the mortality rate accounts for 2.9 Deaths in the United Kingdom, and 5.3 Deaths in united states of America per 100,000 children less than twelve months of age. (1)

In the USA, between 1980 to 1996 an estimated of 1.65 million admissions of children with bronchiolitis happened among patients less than five years of age, 57 per cent of these admissions happened among patients less than six months of age and 81 per cent among children less than one year of age. Admission rates among patients less than one year of age raised approximately 2.4-fold, (from 12.9 to 31.2 per 1000 child between 1980 to 1996).The admission rate for infants with bronchiolitis increased substantially, while the rate of admission of lower respiratory infections was not changed markedly in patients less than 1 year, the ratio of hospitalization for lower respiratory tract disease that associated with bronchiolitis raised approximately (from 22 percent to 47 percent, between 1980 to 1996), and this ratio increased from 5.4 percent to 16.4 percent of overall admissions. (RSV) infection accounts for about 50-80 % of bronchiolitis admissions, between 1994-1996, there was 51, 240 to 81, 985 annual admissions of children less than one year of age with bronchiolitis which was caused by RSV infections. (2)

In the USA, Over the past fifteen years, hospitalization rates for this illness have relatively increased, whereas mortality rates have remained comparatively constant, which may indicate that several of admissions were unjustified or unnecessary, its believed that this elevation of admission rate of bronchiolitis may be related to overdiagnosis of hypoxia by using pulse oximetry devices. in addition to, increased survival of premature babies. (2) IN (UK), it was observed that the admission rate is increasing in England. from 1979 to 2011, around 468138 cases of children with bronchiolitis (less than 1 years) have admitted in hospital for treatment, and in 2011 hospitalization rate was approximately 46.1 per 1000 child (less than 1 years) annually, and from 2004 to 2011 hospitalization rate increased at an average of 1.8% per year.(3)

Pathophysiology

Bronchiolitis is usually caused by acute viral infection most commonly Respiratory syncytial virus (RSV), which accounts for up to 60-80 per cent of all patients with bronchiolitis less than one year of age. (RSV) commonly spread in seasonal basis which occurs during winter seasons that last from October until May. however, other viruses can play role in the aetiology of bronchiolitis such as rhinovirus that accounts for (14–30 percent), human bocavirus (14–15 percent), Influenza, coronavirus, adenovirus, and enterovirus they only account for (1–8 percent). bronchiolitis is sometimes caused by two viruses at the same time in (20–30 percent) of children. However, it usually does not increase the severity of disease .(4)

(RSV) is commonly spread through direct contact with infected respiratory droplets from patients or contaminated surfaces. Infection begins in the upper respiratory tract, then extending to the lower respiratory system within 2-4 days, this virus mainly affects the distal part of the respiratory tract (bronchioles), which results in direct damage to epithelial surface in the small airway and indirect damage to the respiratory system through activating the immune system. RSV infection causes inflammatory responses in the peribranchial area of small airways which include infiltration of various types of white blood cell and oedema.

Accumulation of mucus secretions, injured epithelia tissues and Oedema may result in a varying degree of pulmonary obstruction, hyperinflation and atelectasis, which in turn lead to increased respiratory rate and hypoxemia (decreased oxygen saturation). additionally, bronchoconstriction may happen in children with bronchiolitis however, it has been shown that the role of bronchoconstriction in the pathophysiology of bronchiolitis is inconsiderable. (5) Despite (RSV) infection causes illness during childhood. however, an adult with chronic respiratory diseases or patients with immune deficiency have a high risk to develop RSV infection all-time through the year and they might become a reservoir of this virus .(6)

clinical features

Bronchiolitis usually begins during first 2 to 4 days with signs and symptoms of upper respiratory infection such as runny nose and low-grade fever, after that the infection may extend progressively to affect in the lower respiratory system, and patients may demonstrate sign and symptoms of lower respiratory infection such as cough, tachypnoea and wheezy chest. however, apnoea could be a dominant symptom in very young patients with a history of prematurity (7). The wheezy chest is a distinctive sign in children with bronchiolitis and it is usually an audible sign on chest auscultation in older children. However, in very young children this sign may not be heard and (fine crackles) is the major sign on auscultation (7) . Clinical examination findings in infants with bronchiolitis may include ill appearance, increased respiratory rate, using accessory muscles, retraction, and varying degrees of hypoxia (decreased oxygen saturation). The length of stay in the hospital approximately one day in patients less than 1 year of age and 40 percent of children with bronchiolitis commonly need more than 14 days for resolution of disease. (7,8)

Classification of disease and indications for admission

Children or infants with acute bronchiolitis may attend the emergency department during outbreaks with a broad range of signs, symptoms, and severity, despite there is no uniform scoring system of the severity of bronchiolitis. However, it may be categorized in three gradings which ranges from a mild case of upper respiratory infection to moderate case of lower respiratory symptoms and some patients may reach to a severe case of respiratory failure. The decision to admit patients with bronchiolitis in hospital generally relies on many factors such as: severity of disease, age of patient, lethargic appearance, oxygen saturation less than 92% in room air, respiratory distress and Respiratory rate more than 70 breaths per minute, a child with chronic or immunodeficiency disease. (9) In general the most important causes for hospitalization are feeding difficulty or poor intake, dehydration and significant respiratory distress or failure. (10)

Diagnosis:

The diagnosis of bronchiolitis in children is usually based on associated signs and symptoms and no need for routine or additional tests to make this diagnosis. However, it has been shown that viral test and detecting the type of virus in bronchiolitis may help in reducing the unnecessary use of antibiotics and the length of stay in hospital (10,11) . Status of the patient may change during the stages of infection. therefore, clinical examination and oxygen saturation should be repeated particularly in high-risk patients. Oxygen saturation should be monitored. however, it has been found that the level of oxygen saturation which identified by pulse oximetry may push physician to give oxygen at inappropriate thresholds, which in turn may increase admission rate and length of stay in hospital. In fact, many evidence have demonstrated that intermittent hypoxemia might happen commonly in stable patients with bronchiolitis, in Canadian (RCT) study, it has been found decreased in hospitalization rate when pulse oximetry showed values 3 percent more than the actual oxygen saturation level, this refers that oxygen saturation values that identified by pulse oximetry lead to unnecessary hospitalizations.(12) A similar study performed in the UK showed that lowering oxygen saturation threshold values from 94 percent to 90 percent lead to a decreased length of stay in hospital . (12) A latest study that evaluated oxygen saturation in the home for infants with bronchiolitis has demonstrated that oxygen saturation was approximately 90 percent in the considerable ratio of those infants who were otherwise doing well. (13) .Finally, it seems that continuous oxygen monitoring in children with bronchiolitis resulted in increased admission rate for many unjustified cases.

Beta-2 agonist

Beta-2 agonist medications have produced through process of modification on epinephrine molecules, and since epinephrine affects both Alpha and Beta (1 and 2) receptors, this modification helped in creating a new molecule that affects mainly on beta-2 receptors which located on smooth muscles of small airways to stimulate bronchodilation without activating beta-1 receptors on heart muscle. Beta-2 agonists usually categorized into 3 groups: short-acting, Long-Acting and ultra-long-acting. Short-acting beta-2 agonists such as (albuterol/salbutamol) that have Onset of action less than 5 minutes and remains for 3-6 hour, usually given to the patient via inhalation route or sometimes via the oral route. (14) . Beta-2 agonists have undergone many modifications to improve their efficiency and reduce side effects such as tachycardia, muscle tremor, Headache, and nausea.The common use of beta-2 agonists in emergency departments came from the fact that they succeeded in fighting the wheezing in asthma, which is also a distinctive sign in children with bronchiolitis. However, unlike asthma, the pathophysiology of wheezing in bronchiolitis is the result of submucosal oedema, accumulation of dead cells and mucus secretion in small airways rather than bronchoconstriction which may explain the different efficacy of using beta-2 agonist between the two diseases. (15)

Treatment

Although, treatment of bronchiolitis after Admission is still supportive care and it includes rehydration, providing humidified oxygen, Airway suction, and assisted ventilation if needed. however, the use of beta-2 agonists particularly (albuterol/salbutamol) in the emergency department is still a common clinical intervention in children with bronchiolitis and the available evidence in the medical literature about the efficacy of these treatments are conflicting.in addition to, Increased admissions rates despite use of beta-2 agonist make this popular therapy is controversial (16). Finally, bronchiolitis in children is usually a self-limiting illness with very good long-term prognosis. However, accumulating evidence suggests that infant who had hospitalization because of moderate to severe RSV infection, have a high risk to develop recurrent wheezy chest incidents in later life. (17)

Aims/Objectives

Due to the fact that that hospitalization rate has been increasing during the last 20 year and various kind of treatments has been used, including beta-2 agonists which are still used in children with bronchiolitis and though there are many suspicions about their efficacy. Therefore, the aim of this study is to conduct a literature review for available (RCTs) that studied the efficacy of beta-2 agonists (albuterol/salbutamol) in children less than 2 years of age with bronchiolitis which may help in answer the following questions:

Do beta-2 agonists reduce admission rates or improve oxygen saturation and respiratory rates in children with bronchiolitis?.

In fact, those secondary outcomes were chosen in this review because they play an important role in the decision of admission. (18) Study by (Mallory et al. 2003) that included 812 physicians in survey regarding the factors which influence on decision for hospitalization, results showed that 43 % of physicians relied on oxygen saturation values equal or less than 94 % plus respiratory rates 50/min, whereas 58 % of physicians relied on oxygen saturation values that equal or less than 94% plus respiratory rates 65/min for admission.

Methods and Search strategies

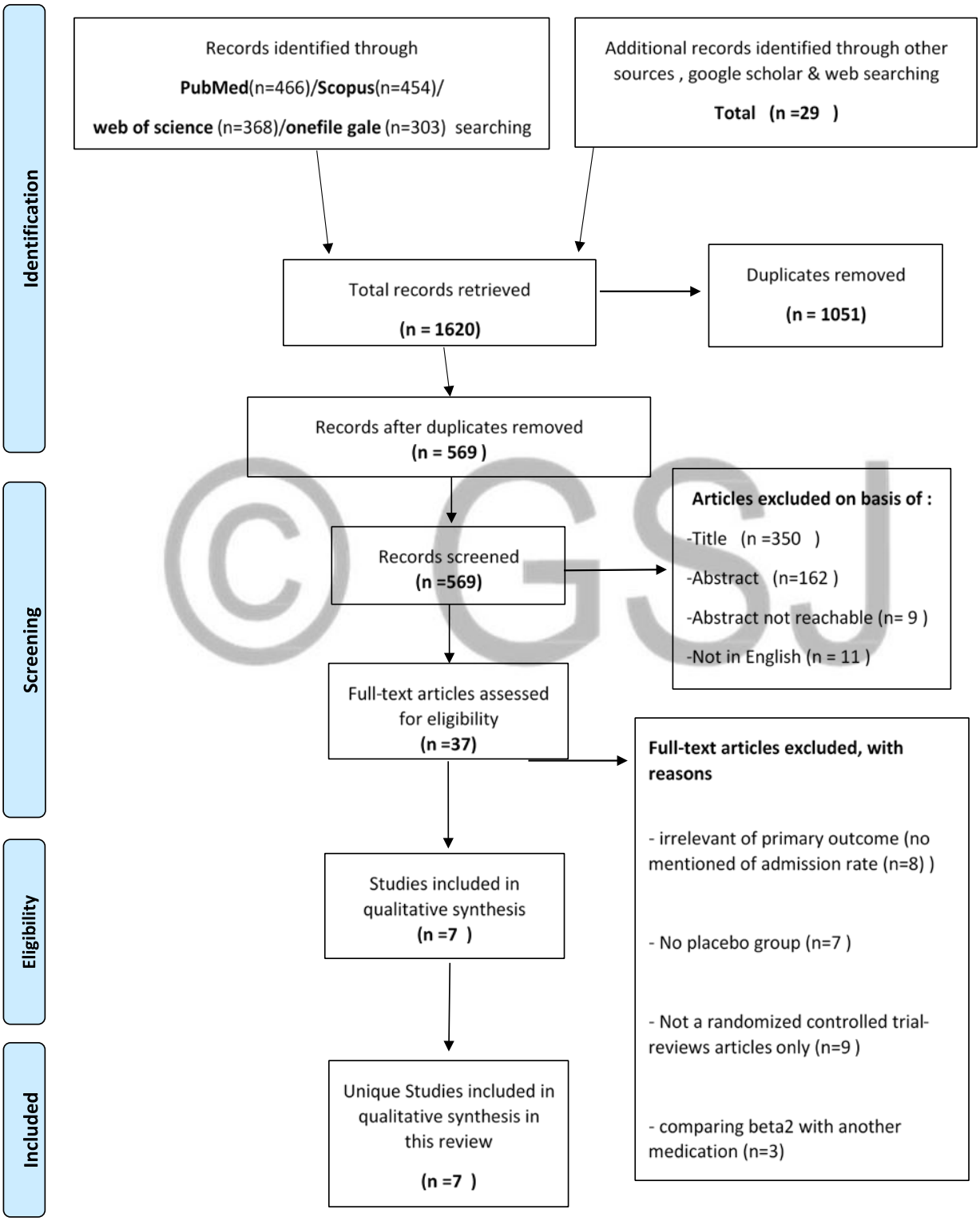
To identify articles of beta-2 agonist treatment for bronchiolitis, four medical databases: PubMed, Scopus, web of science and OneFile gale were searched using the following keywords (bronchodilator – bronchiolitis - beta 2 Agonist - salbutamol – albuterol) , in search tools , active filters were applied on the results and bronchiolitis subject was chosen to remove any other results that are not in the subject of interest of this review and keep focusing on bronchiolitis subject.
A total of 1591 articles has been found, Additional 30 articles were found by a search of the references from google scholar and web searching, 569 studies remain after the removal of duplicated studies in the medical databases.
in this literature review, the studies that consistent with the following criteria were only included:

Study design: Randomized controlled trail (RCT).
The population of interest: Infants and children less than 2 years of age with bronchiolitis.
Interventions: Use of Beta 2 Agonist either via nebulization route or oral route.
Comparators: Comparing beta-2 agonists group receptors with placebo group receptors.
Outcomes: Hospitalization rate, oxygen saturation and respiratory rate.
Date of the studies: no restriction
Language: Studies in the English language

All articles that meet the above inclusion criteria were included. Whereas, articles that only studied the efficacy of beta and alpha agonist such as (epinephrine) and articles that only compare beta-2 agonists with other interventions were excluded, in addition to Studies without a placebo group and studies with unobtainable as full text were also excluded. Of 569 retrieved articles, 532 were excluded (350 articles upon reading their titles, 162 articles upon reading their abstracts, abstracts of 9 articles were not reachable and 11 articles were not in the English language). 37 articles have remained for full reading and assessment, of those articles (8 ar-

ticles had irrelevant primary and secondary outcomes, 7 articles did not include a placebo group to compare against, 9 articles were not randomized trials, 3 articles only compare beta-2 agonists with other medications and full text of 3 articles were not reachable).

PRISMA diagram



Results

This literature review based on 7 randomized controlled trials with a total of 670 patients less than two years of age and those (RCT)s were conducted between 1990 to 2011 and they relied on comparing between beta-2 agonist (albuterol/salbutamol) group with a placebo group to assess the efficacy of Albuterol in children with bronchiolitis. The results of these studies are summarized as follows:

In 1990, (Schuh et al) have conducted a Randomized Control trail study to assess efficacy of nebulized albuterol in bronchiolitis, 40 patient (from 6 weeks up to 2 years of age) were included ,who had symptoms of acute bronchiolitis and wheezy chest for the first time , they were distributed into 2 groups :
(Group 1 n=21 patients) they received 3 doses of nebulized albuterol (0.15 mg/kg/dose) apart 1 hour
(Group 2 n=19 patients) they received 2 doses of nebulized normal saline apart 1 hour In this study, they focused on the following outcome: oxygen saturation, respiratory rate and heart rate, hospitalization rate.in addition to, wheeze and accessory muscle score. they have measured outcomes before and after giving doses at 0, 60, and 120 minutes. significant improvement was observed in group 1 which was in the following outcomes: oxygen saturation (0.71% increase in group 1 vs 0.47% decreased in group 2; p = 0.01) respiratory rates (16.2 % decreased in group 1 vs 15.5% decreased in group 2; p= NS) and after the second dose oxygen saturation (0.76% increase in group 1 vs 0.79% decreased in group 2; p = 0.015) respiratory rates (19.6% decreased in group 1 vs 8.0% decreased in group 2; p = 0.016) regarding admission rate: six patients were admitted in hospital after received the aboovementioned treatment (15 %) - four patients from group 1 and two from of group 2 , hospitalization rate was low and there was no statistically significant difference between the two groups [odds ratio 2, P= 0.45, confidence interval (CI) 95% (0.32 - 12.41)] . The author concluded that use of beta 2 agonist (Albuterol) is an effective intervention in children with bronchiolitis.(19)

Another RCT study was conducted by ***(Klassen et al 1991)*** to evaluate the efficacy and safety of nebulized salbutamol in children with bronchiolitis***,*** 83 patients (from 1 to 21 months of age) were assigned in two groups
(group 1 n =42 patients) were given 2 doses of nebulized salbutamol (0.02 ml/kg) ,30 minutes apart
(group 2 n=41 patients) were given 2 doses of nebulized (0.02 ml/kg) normal saline placebo, 30 minutes apart
outcome measures were: respiratory rate, oxygen saturation, heart rate, clinical assessment
(degree of wheezing and retraction) at 0, 30, 60 minutes and admission rate The study showed that group 1 had a significant improvement in clinical assessment. however, No significant changes in oxygen saturation [at 60 minute, (95±4 %) in salbutamol group vs placebo (95±4 %) - P (0.74)] and No significant changes in Respiratory rate (per min) [at 60 minute (50±11) in salbutamol group vs placebo (50±11) - P(0.88)]. additionally, there were no noticeable differences in the number of admissions between the two groups [odds ratio 1.22, P= 0.67, (CI) 95% (0.47 - 3.16)] and the results of hospitalization rates were as follows: 24 patients were admitted, 13 patients from group 1 and 11 patients from group 2 .
(Klassen et al) concluded that the use of albuterol in patients with bronchiolitis is an effective and safe treatment. (20)

RCT by ***(Schweich et al 1992)*** included 25 patient less than 2 years of age who had wheezy chest, to assess the efficacy of albuterol in wheezy infants. participants were enrolled randomly in two groups :
(group 1 n =13 patients) received 2 doses of nebulized salbutamol (0.15 mg/kg) ,30 minutes apart
(group 2 n=12 patients) received 2 doses of nebulized normal saline -placebo, 30 minutes apart
The study focused on the following outcomes measure: wheezy and retraction score, heart rate, respiratory rate, oxygen saturation, at 0, 30, 60 minutes and admission rate. significant improvement was observed in wheezing and total score ($p<0.05$) of group 1 , although there was an initial decreased in oxygen saturation in group 1, however, it improved after the second dose.
results of respiratory rate and heart rate were similar in two groups and mean changes were as follows: Oxygen saturation [after the second dose (+2.4) in salbutamol group vs placebo (0.4), P (not significant)].
Respiratory rate [after second dose (-1.4) in salbutamol group vs placebo (-0.5), P(not significant)] . additionally, no significant differences were noted in admission rates [odds ratio 0.30, P= 0.16 , (CI) 95% (0.05 - 1.66)] and the results of the admission rate were as follows: 6 patients (50%) of the placebo group and 3 patients (23%) of salbutamol group were admitted in the hospital. eventually, the author concluded that albuterol is an effective treatment in infants with bronchiolitis by relying on wheeze score and the total score. (21)

(Gadomski et al 1994) have conducted randomized double-blind placebo-controlled trial, to evaluate the efficacy of albuterol in children with bronchiolitis, ***88*** patients were included, age (from 0 to 15 months) who had sign and symptoms of bronchiolitis and wheezy chest for the first time and they were assigned in four groups :
(group 1 n =22 patients) received 2 doses of nebulized albuterol (0.15mg/kg) ,30 minutes apart.
(group 2 n=23 patients) received 2 doses of nebulized normal saline, 30 minutes apart.
(group 3 n=19 patients) received 1 dose of oral albuterol (0.15mg/kg).
(group 3 n= 24 patients) received 1 dose of oral placebo.
they focused on the following outcomes: oxygen saturation, respiratory rate and heart rate infant state and admission rate. And they measured outcomes before and after giving the doses at 0,30,60 minutes. no significant differences of mean changes were observed between four groups except increased heart rate that was observed in group 3 [15 beats per minute - P (0.005)]. additionally, there were no significant changes in hospitalization rate between group 1 and 2 [odds ratio 1.33 , P= 0.76 , (CI) 95% (0.19 - 9.02)] , or between oral albuterol group and placebo group [odds ratio 0.33 , P= 0.76 , (CI) 95% (0.03 - 3.20)], and the results of admission rate were as follows: 10 patients of 88 admitted in hospital for additional treatment, 3 patients from group 1 (14%) - 2 patients from group 2 (11%) - 1 patient from group 3 (6%) and 4 patients from group 4 (18%)
(Gadomski et al) concluded that albuterol and placebo treatment have the same efficacy in children with bronchiolitis. (22)

Between 2000 and 2004 ***(Ralston et al. 2005)*** studied the effect of nebulized albuterol and Epinephrine on children with bronchiolitis, 65 patients (from 6 weeks to 2 years of age) were assigned in three groups
(group 1 n =23 patients) received 3 doses of (5 mg) nebulized albuterol, 30 minutes apart.
(group 2 n=17 patients) received 3 doses of (5 mg) nebulized epinephrine, 30 minutes apart.
(group 3 n=25 patients) received 3 doses of placebo.
The study included primary and secondary outcomes which are admission rates, need for additional oxygen in home, oxygen saturation and clinical score. it showed no significant differences in all measured outcomes among groups. Moreover, the hospitalization rate was almost similar in all groups [odds ratio 0.87, P= 0.82, (CI) 95% (0.27 - 2.81)] , and the results of the admission rate were as follows: 14 patients (61%) of group 1, 10 patients (59%) of group 2 and 16 patients (64%) of group 3 were admitted for treatment. The authours concluded that albuterol, epinephrine and placebo had similar effects on final outcomes and no significant differences were noted in all measured outcomes among groups. (23)

In 2010 study by ***(Anil et al.)*** evaluated the response of infants with moderate bronchiolitis to nebulized salbutamol, epinephrine and 3 %saline, 186 infants (age from 1,5 – 24 months) how had wheezing for the first time were assigned to five groups :

(group 1 n =38 patients) were given 2 doses of nebulized epinephrine(1.5mg) +normal saline
(group 2 n=39 patients) were given 2 doses of nebulized epinephrine (1.5mg) + 3% saline
(group 3 n=36 patients) were given 2 doses of nebulized salbutamol(2.5mg) +normal saline.
(group 4 n= 36 patients) were given 2 doses nebulized Salbutamol(2.5mg) + 3%saline.
(group 5 n= 37 patients) were given 2 doses of normal saline.
the second dose was given after 30 minutes. Outcomes measure included : admission rate, oxygen saturation, heart rate and Clinical score, those outcomes were evaluated at 0, 30, 60, and 120min. although, there were significant differences between results at 120 min and baseline results ($P<0.05$). however, no significant differences of variables outcomes were found among groups ($P>0.05$). in addition to, the hospitalization rate was as following: 0 patient was admitted from group 1,4 and 5, one patient from group2 and one patient from group 3. eventually, the study concluded that the efficacy of all types of treatments on final outcomes in infants with moderate bronchiolitis was similar among the five groups. (24) Between October 2009 and March 2010 a randomized, double-blind, prospective study was conducted by ***(Ipek et al. 2011)*** to investigate the efficacy of salbutamol and 3 % saline in infants with bronchiolitis, 120 participants less than 2 years of age were assigned to 4 groups :
(group 1 n = 30 patients) received 2 doses of nebulized salbutamol +normal saline (group 2 n=30 patients) received 2 doses of nebulized salbutamol+ saline 3 %.
(group 3 n=30 patients) received 2 doses of nebulized saline 3 %. (group 4 n= 30 patients) received 2 doses
of nebulized normal saline

outcomes measure of the study included: oxygen saturation, heart rate and clinical severity score in addition to, admission rate. primary outcomes were measured before and after treatment, also at 48 and 72 hours. The study showed that Respiratory rate and oxygen saturation have improved in all groups without significant difference between the four groups. Furthermore, no significant differences were noted in hospitalization rate between group 1 and placebo group 4 [odds ratio 0.55 , P= 0.45 , (CI) 95% (0.12 - 2.56)] , or between oral salbutamol group 2 and placebo group 4 [odds ratio 0.64 , P= 0.64 , (CI) 95% (0.09 - 4.15)] and the result of hospitalization was as follows: 13 of 120 patients were admitted in hospital and they distributed as follows: three patients (10%) from group 1 , two patients (6.7 %) from group 2 , three patients (10%) from group 3 and five patients (16.7 %) from group 4. (Ipek et al) concluded that effectiveness of all type of treatment were similar and No preference was existing among used medications. (25)

Discussion

In this review, the emphasis was placed on (albuterol/salbutamol) which is the most common beta-2 agonist medication that usually used in the emergency department for children with bronchiolitis. medical databases were searched for the (RCT) studies that include primary and secondary outcomes which evaluate the efficacy of beta- 2 agonists on hospitalization rate, oxygen saturation and respiratory rate in children with bronchiolitis. 7 unique RCT studies found from 1990 to 2011 and the main findings of these studies were summarized as follows:

Hospitalization rates:

All included studies in this literature review had outcomes measure refer clearly that (Albuterol/Salbutamol) did not reduce admission rates in beta-2 agonist group compared with the placebo group. therefore, 100% of RCTs in this study concluded that beta-2 agonist do not reduce hospitalization rate in children with bronchiolitis (16.5% in Beta-2 agonist group versus 20% in placebo group, [odds ratio 0.74 , P = 0.20 , 95% CI (0.474 to 1.169)] total patients = 501).
(table shows the admission rates in each study)

Name of Study / date	Beta-2 agonist group		Placebo group		Odds ratio , Z statistic , P , (95% CI)
	Number of patients	Number of admitted patient (%)	Number of patients	Number of admitted patient (%)	
Schuh et al 1990	21	4 (19 %)	19	2 (10.5%)	2, 0.74 , P= 0.456 ,(0.322 - 12.414)
Klassen et al 1991	42	13 (30%)	41	11 (26.8%)	1.22 , 0.41 , P= 0.678 ,(0.472 - 3.165)
Schweich et al 1992	13	3 (23%)	12	6 (50%)	0.30 , 1.37 , P=0.169 , (0.053 - 1.668)
Gadomski et al 1994 / nebulization	21	3(14%)	18	2 (11%)	1.33 , 0.29 , P = 0.768 , (0.197 - 9.020)
Gadomski et al 1994 / oral	15	1(6%)	22	4 (18%)	0.32 , 0.96 , P = 0.333 , (0.032 - 3.205)
Ralston et al. 2005	23	14(61%)	25	16 (64%)	0.87 , 0.22 , P = 0.823 , (0.271 - 2.818)
Anil et al. 2010 – salb+ 3%	36	0 (0)	19	0 (0%)	Not estimable
Anil et al. 2010 – salb+ 0.9%	36	1(2.7%)	18	0 (0%)	1.56 , 0.27 , P = 0.787 , (0.060 - 40.305)
Ipek et al. 2011 / salb + 0.9% saline	30	3(10%)	30	5 (16.7%)	0.55 , 0.75 , P = 0.451 , (0.120 - 2.568)
Ipek et al. 2011 / salb + 3% saline	30	2 (6.7%)	30	3 (10%)	0.64 , 0.46 , P = 0.642 , (0.099 - 4.153)
Total events	***267***	***44 (16.5%)***	***234***	***49 (20%)***	***0.74 , 1.27 , P = 0.201 , (0.474 - 1.169)***

Total events: 44 (Beta-2 agonists), 49 (Placebo)
CI: Confidence Interval
OR: odds ratio
P: Significance level
Z statics: standard score

Oxygen saturation and respiratory rates:

Although three studies (19,20,21) of seven concluded that Albuterol is an effective treatment in children with bronchiolitis. However , only one of them (Schuh et al 1990) observed some transient improvement in oxygen saturation and respiratory rates , whereas the other two studies (Klassen et al 1991), (Schweich et al 1992) showed that there was no significant improvement in oxygen saturation or respiratory rate in beta-2 agonist recipients compared with placebo recipients. In addition to, the latest studies (22,23,24,25) demonstrated that the treatment did not improve oxygen saturation or respiratory rates in beta-2 agonist group. therefore, 6 studies of 7 (85%) showed clearly that beta-2 agonist did not improve oxygen saturation or respiratory rate in beta-2 agonist group compared with placebo group.

Risk of bias in trails:

Most of the included trials in this review had a clear definition of bronchiolitis and clear determination of, study design, Population of interest, type of intervention, comparison groups and outcomes. in addition to, a clear inclusion and exclusion criteria in term of selection of patients. in fact, the risk of bias was low because the included trials were double-blinded, allocation sequence was created sufficiently, patients were assigned randomly to groups and treatment was sufficiently concealed. additionally, the reports included all anticipated outcomes without any selectivity. However, some included trails had methodologic issues such as lack of randomization and that appear clearly in (Ipek et al. 2011) trail who have assigned patients to the group in consecutive order, whereas Three trails have used computer software for randomization and some trails they were not clear about how the randomization have done.

Limitations of included studies:

There are several limitations and missing points were noted in included (RCT)s such as, the numbers of patients that assigned to any group were generally small size.
Not all (RCT)s have depended on virologic confirmation test in diagnosis.
In fact, four trails of seven have performed a viral test to confirm or rule out diagnosis of bronchiolitis and viral test was positive in 71 % of children in (Schuh et al) trail and it was positive in 85 % of patients in (Klassen et al 1991) trail, in (Gadomski et al 1994) trail 85 % of patients had positive viral test, whereas viral test was only positive in 40 % of enrolled patients in (Schweich et al 1992) trail . The rest of trails (23,24,25) have relied on only clinical manifestations of the disease to make a diagnosis of bronchiolitis. Which could indicate that some patients with another aetiology of the disease have been included in those trails.

Two (RCTs) did not obviously mention if included patients had the wheezy chest for the first time or not (21,20), as it is well known, patients with a background of asthma might have a better response to beta-2 agonists. therefore, these studies may have included asthmatic patients in their groups as a result of inadequate inclusion and exclusion criteria. And this argument may be supported by hospitalization rate and duration of hospitalization which did not change in those studies.
To emphasize this point, a study by (Sanchez et al) found that older patients with bronchiolitis particularly above one year of age who had a sinusoidal wheeze pattern, they generally showed a better response to bronchodilator and that because their wheezing sign might be an early manifestation of asthma. (26)

Another limitation point that was not adequately discussed in included trails. whether participants have received any type of treatment before enrolment or not? which may affect the measured outcomes. for instance, giving humidified oxygen might alter oxygen saturation, respiratory rates and may give unreliable results. Moreover, in some trails (20,21,22,25) they did not determine the duration of illness upon enrolment in the study. however, in other studies (19,23,24) they clearly determined the duration of illness and severity of disease.

None of the included trials discussed the impact of the administration methods of medication on final clinical outcomes in patients with bronchiolitis? as we know the mist form of beta-2 agonists can be delivered to patients in two ways either via metered-dose inhalers (MDIs) or nebulizer machines. However, in included trails, almost all beta-2 agonists were provided to patients via ne-

bulizer machine, in fact there are several studies showed that children who received salbutamol via metered-dose inhaler devices (MDI) had better response than those who received medication via nebulizer machine. (27,28)

Comparison the findings of this review with other published studies

It is believed that conflictions among some old and latest studies about the efficacy of beta-2 agonists in bronchiolitis are the result of strategy weakness in studies that observed benefits of using beta-2 agonist. in fact, some of these studies depended on clinical scores as the primary outcome measure and despite there was a significant improvement in clinical scores, it was on a short-term basis and clinical significance of these findings was uncertain. Moreover, those studies also have ignored to discuss what is the impact of the physiological status of patient on clinical scores such as respiratory rate, heart rate and even oxygen saturation. as well-known, heart rate and respiratory rate may change significantly according to patient status during (sleeping, crying, waking ...etc). therefore, it is probably that inappropriate interpretation of clinical score might have occurred. (29)

Several recent studies and systematic reviews have assessed the efficacy of beta-2 agonist in children with bronchiolitis and they did not find any true benefits of beta-2 agonists and they did not encourage the routine use of beta-2 agonist in children with bronchiolitis. In 2004 systematic review by (King et al) have evaluated the efficacy of common medications in children with bronchiolitis, 13 (RCTs) that comparing beta-2 agonist group with the placebo group have included and various type of outcomes were measured such as oxygen saturation length of stay in hospital, admission rate and clinical scores , none of those (RCTs) showed any significant differences between Albuterol group and placebo group and study concluded that there is no evidence support using of beta-2 agonist in children with bronchiolitis. (30)

In general, (RCT)s in this review have conducted on mild to moderate cases of bronchiolitis. However, it was also found that children with moderately severe bronchiolitis had the same response to beta-2 agonists, between 1995 - 1996 study of (Dobson et al) that conducted to evaluate the response of infants with (moderately severe) bronchiolitis to albuterol nebulization and if treatment can help in accelerating recovery or improving clinical outcomes in enrolment patients, the study included a total of 52 patients less than 2 years of age in a prospective double-blind, placebo-controlled randomized trial. outcomes measure included: duration of time needed to reach discharge criteria , oxygen saturation , length of hospital stay and side effects, study showed no significant differences between albuterol group and placebo group and they concluded that the use of albuterol did not lead to enhance recovery of patients with bronchiolitis and it did not lead to significant improvement in oxygen saturation or in the rest of outcomes (31).

The findings in this literature review also compatible with the most recent systematic review in Cochrane library that has conducted by (Gadomski et al 2014) to evaluate the efficacy of bronchodilator in infant with bronchiolitis, 30 Randomized controlled trials with total of 1992 participants were included in this review , 21 trails represent 70 % of all included trails (11 inpatients and 10 outpatient studies) , this study demonstrated that the use of bronchodilator treatment did not improve oxygen saturation [(MD) -0.43, 95% confidence interval (0.92 to 0.06,) n = 1242 patients]. And did not reduce hospitalization rates [11.9% in bronchodilator group vs 15.9% in placebo group, odds ratio 0.75, 95% - CI (0.46 to 1.21) n = 710 patients). (32) In the same context of this review findings, American
Academy of paediatrics (AAP) published in 2006, a new Guidelines on Diagnosis and Management of bronchiolitis, they encouraged physician not to routinely use bronchodilator in patients with bronchiolitis and In a follow-up study in 2014, (AAP) recommended not to use albuterol even as a trial dose in children with bronchiolitis , because the effectiveness that was noticed in some patients is usually transient and it does not lead to a significant changes in natural course of disease and it does not reduce length of stay in hospital or improve clinical status of patients. (33)

It has become increasingly clear that beta-2 agonist (salbutamol) has no true benefits in children with bronchiolitis and the most acceptable explanation might be connected to pathophysiology of disease itself , it is well known that viral infection in bronchiolitis affects
small airways, which leads to varying degree of bronchioles obstruction, despite Bronchoconstriction may happened in bronchiolitis , however the main mechanism of respiratory obstruction is the result of accumulation of damaged epithelial tissues and different types of dead cells, excessive respiratory secretions and oedema. Additionally, these quantities of accumulations in small airways play its role in two ways, the first one is a physical obstruction in bronchioles. secondly, it prevents mist of medication reach to its distal receptors in the respiratory system. Moreover, some references suggest that infant might have an immature respiratory system which may reflect in insufficient beta-2 agonist receptors and inadequate response of immature smooth muscle in the respiratory system.(35,34)

Even though there are many studies were conducted on this subject. however, no articles have been found indicating that beta-2 agonists might reduce admission rates in children with bronchiolitis.

Oral albuterol Versus nebulization

No differences have been found between the oral or nebulized form of albuterol. In fact, the use of oral Albuterol rather than nebulization form did not achieve any benefits for the patient with bronchiolitis, which was demonstrated in (Gadomski et al) study and supported by (Gupta et al.) study that conducted in 2008 to evaluate efficacy of oral salbutamol in infants with mild bronchiolitis , 140 infants were assigned in 2 groups to receive either oral salbutamol (0.1 mg/kg/dose) or placebo. And results were as follows: time to recovery was similar in both group (group 1 [6 (0, 5 to 7) day] vs group of placebo [5 (1, 4 to 6)] .additionally, there were no significant differences hospitalization rates, time to recovery and duration of symptoms. (36)

Possible adverse effects and a negative impact of beta-2 agonist

In the field of adverse effects, it is well known that beta-2 agonists have side effects, (Schuh et al) And (Klassen et al) observed increased heart rate in albuterol group patients, while study of (Gadomski et al) reported that some patients in oral albuterol group had a significant increase in heart rate.in addition to, another patient had side effects such as flushing face, hyperactivity, tremor. these findings of side effects of beta-2 agonist are consistent with the conclusion of (Mukherjee et al) retrospective study which conducted in 2014, to evaluate the potential side effect of salbutamol on the cardiovascular system in children with bronchiolitis. A total of 201 patients were assigned to groups to receive either salbutamol, placebo or ipratropium bromide. the study found a significant increase in heart rate in patients who received salbutamol. since beta-2 agonist is not an effective treatment in children with bronchiolitis and these medications may be accompanied with significantly increased heart rate. therefore, putting patient under additional stress of medication besides disease itself may be considered unjustified management. (37)

On the other hand, some studies have reported a negative impact of the beta-2 agonist on oxygen saturation In infants with bronchiolitis. For instance ,double-blind randomized crossover Study by (Ho et al. 1991) that assessed efficacy of albuterol on oxygen saturation in infants with bronchiolitis, 21 infants (from 3 weeks to 6 months of age) with bronchiolitis enrolled to receive two doses of normal saline and albuterol alternatively , Oxygen saturation were assessed before and then after each dose over 30 minute continuously , the study found significant decreasing in oxygen saturation after albuterol nebulization in first and second dose, which happened at peak duration of Action of salbutamol. (38)

Treatment that might help in reducing the admission rate in bronchiolitis.

A promising combination therapy of nebulized racemic epinephrine and dexamethasone might help in reducing admission rate in children with bronchiolitis, this evidence came from recent, large multicentre trial which conducted in paediatrics emergency departments in Canada ,this trail included 800 infants (from 6 weeks to 12 months) who had diagnosis of bronchiolitis to assess the efficacy of epinephrine dexamethasone , on hospitalization. Patients were enrolled to one of four groups to receive one of the following treatments: (nebulized epinephrine + oral dexamethasone) or (nebulized epinephrine + placebo) or (nebulized placebo and oral dexamethasone) or (nebulized placebo + oral placebo). The authors found significant decrease in admission rate in group 3 that received nebulized epinephrine (3 ml of epinephrine in a 1:1000) plus oral dexamethasone (1.0 mg /kg in first days then 0.6mg/kg for 5days), and study concluded that combination therapy of Albuterol plus dexamethasone reduce the admission rate in children with bronchiolitis. (39)

Finally, it is pretty much noticeable to suggest that though bronchiolitis is a very common cause of wheezy chest in children and though there are many studies published about this subject. however, essential controversy about the best initial treatment and management still existing. Many recent studies have not succeeded to prove any true benefits of using of beta-2 agonist in bronchiolitis , studies that discussed in this literature review would seem to support the latest guidelines of (AAP) for management and treatment of bronchiolitis , and It has been observed that this direction in management has led to decreased cost of unnecessary treatment , decreased rates of use of Beta-2 agonist and reduced length of stay in hospital without increasing readmission rates and helped in Reduce unnecessary exposure to side effects of treatments. (40)

Conclusion

Though the use of beta-2 agonist (albuterol or salbutamol) in children with bronchiolitis remains controversial, and most of the evidence refers to the poor or no response. the result of this literature review adds to available evidence that the use of beta-2 agonist (albuterol/salbutamol) in children with bronchiolitis do not reduce admission rate. Additionally, they do not lead to a long term improvement in oxygen saturation or improve in respiratory status of patients.

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