Commentary

Do bronchodilators have an effect on bronchiolitis?

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Abstract

Over the past 12 years there have been 12 randomised control trials, involving 843 infants, evaluating the effect of salbutamol or albuterol on bronchiolitis. Of these, nine (75%) showed that bronchodilators had no effect. In three studies a small transient improvement in the acute clinical score was seen. Ipratropium bromide had no significant effect. There have been five recent randomised trials involving 225 infants, evaluating the effect of nebulised adrenaline (epinephrine) on bronchiolitis. All five (100%) have shown significant clinical improvement, with reductions in oxygen requirement, respiratory rate and wheeze after nebulised adrenaline. Two showed lower hospital admission rates and earlier discharge with adrenaline. A significant improvement in pulmonary resistance was observed after nebulised adrenaline but not after salbutamol or albuterol. Currently there is no compelling evidence that bronchodilators have a role in the routine management of infants with bronchiolitis. There is better evidence for the use of nebulised adrenaline.

Keywords albuterol, bronchiolitis, nebulised adrenaline, pulmonary function tests, salbutamol

In this issue of *Critical Care*, Totapally and colleagues [1] evaluate the effect of albuterol on tidal breathing loops of 20 infants with respiratory syncytial virus (RSV) bronchiolitis. They found that the wheeze score and the pulmonary function tests were not significantly affected by albuterol. This is the latest of 12 randomised controlled trials in 12 years [2–12], involving 843 infants, that evaluated the effect of bronchodilators on bronchiolitis. After so many trials, have we resolved whether bronchodilators have a role in the management of bronchiolitis, and have pulmonary function measurements been helpful?

Salbutamol, albuterol and ipratropium bromide

Of the 12 most recent randomised controlled trials published in English, evaluating the effect of salbutamol or albuterol on bronchiolitis, nine (75%) showed that bronchodilators had no effect. In three of these studies, some difference had been observed [3,11,12], yet it resulted in only a small transient improvement in the acute clinical score and had no effect on hospital admission rates or duration of stay in hospital. In one of these three studies [11], ex-premature infants who might have had some mild underlying chronic lung disease, which might have resulted in the response to bronchodilators, were not excluded. Several studies reported an increase in heart rate [12] or a decrease in oxygen saturation [3] after salbutamol or albuterol.

The effect of ipratropium bromide (either alone or in combination with salbutamol or albuterol) on bronchiolitis has been evaluated in four recent randomised controlled trials [5,6,9,13] and none has shown any significant effect.

Nebulised adrenaline

In contrast, there have been five published randomised controlled trials in the last 10 years, involving 225 infants, evaluating the effect of nebulised adrenaline (epinephrine) on bronchiolitis [7,14–17]. All five (100%) have shown significant clinical improvement in infants with bronchiolitis, with decreases in oxygen requirement, respiratory rate, wheeze and retractions. Menon [14] showed lower hospital admission rates, and Bertrand *et al.* [15] found that the group

RSV = respiratory syncytial virus; t_{PTEF}/t_E = exhaled time to reach peak expiratory flow as a fraction of total expiratory time; V_{maxFRC} = maximal flow at functional residual capacity produced by forced expiration as a result of a rapid chest compression; V_{PTEF}/V_E = tidal volume exhaled at peak tidal expiratory flow as a fraction of total tidal volume.

given nebulised adrenaline were discharged from hospital earlier. A significant improvement in pulmonary resistance was also observed [16]. The incidence of side effects is no more frequent with nebulised adrenaline than with salbutamol. The 90-minute heart rate was often significantly lower in the adrenaline group, and although pallor was noted more frequently it was transient and of no known clinical significance [14].

Pathophysiology

These results suggest that mucosal swelling and mucous plugging make a greater contribution to the increased airway resistance observed in bronchiolitis than constriction of bronchial smooth muscle. Barr *et al*. [18] found a beneficial effect of inhaled adrenaline in an infant with RSV bronchiolitis who was also receiving β-adrenergic receptor blockade with propranolol. This indicates that it was most probably the α-adrenergic stimulation that was improving airway obstruction by inducing arteriolar vasoconstriction in the airway mucosa and thus reducing bronchial mucosal thickness.

Pulmonary function tests

Of the 12 randomised studies evaluating the effect of bronchodilators on bronchiolitis, only in those by Totapally *et al.* [1] and Sly *et al.* [10] were any pulmonary function measurements made. Totapally used tidal breathing flow-volume loops to assess the effect of albuterol on infants with bronchiolitis, and they found no significant change. Two main calculations were made: the exhaled time to reach peak expiratory flow as a fraction of total expiratory time (t_{PTEF}/t_E) and the tidal volume exhaled at peak tidal expiratory flow as a fraction of total tidal volume (V_{PTEF}/V_E).

The time needed to reach peak tidal expiratory flow is highly influenced by the activity of the laryngeal abductors and adductors, abdominal and intercostal expiratory muscles, post-inspiratory activity of the diaphragm and intercostal muscles, and vagal nerve tone [19,20]. Changes in these muscle activities could cause significant alterations in t_{PTEF}/t_E independently of changes in the resistance and compliance of airways and lung. Thus t_{PTEF}/t_E is an insensitive measure of airway function in infants and children in comparison with V_{maxFRC} (maximal flow at functional residual capacity produced by forced expiration as a result of a rapid chest compression) and other more invasive techniques [19].

Sly *et al*. [10] performed a randomised trial of salbutamol in infants with bronchiolitis and measured V_{maxFRC} and found no significant change.

Sanchez [16] also conducted pulmonary function tests in a crossover trial comparing salbutamol with racemic adrenaline. As in other studies, administering salbutamol resulted in no change, whereas adrenaline significantly decreased pulmonary resistance. Sanchez *et al*. used a more invasive technique, measuring transpulmonary pressures (with an oesophageal catheter), flow and volume to determine pulmonary resistance by a least-mean-square technique. They excluded breaths in which the leak was greater than 10%, the correlation coefficient was less than 0.95 or the tidal volume was less than 0.5 ml/kg, to eliminate the analysis of shallow breaths and artefacts.

Leaks around the mask or around an uncuffed endotracheal tube can cause major errors in the pulmonary function measurements and lead to gross overestimation of compliance and resistance [21]. The inspired and expired volumes need to be within 10% of each other to allow an accurate analysis. Totapally *et al*. did not specify the minimum acceptable leak in their study. Ideally, absolute lung volume should also be measured to help in the interpretation of resistance changes; however, this is invasive and difficult to perform.

Conclusion

Although Totapally and colleagues should be commended for performing pulmonary function measurements to assess further the effect of albuterol on infants with bronchiolitis, the pulmonary function results need to be interpreted with a degree of caution. However, in view of the general lack of effect of bronchodilators in bronchiolitis in other studies, I do not think that any significant effect of albuterol on pulmonary function was missed in this study. It also highlights the urgent need for a simple non-invasive test that can measure lung function in infants more accurately.

In summary, there is no compelling evidence that bronchodilators have a role in the routine management of infants with bronchiolitis. There is better evidence for the use of nebulised adrenaline, which results in a reduction of the airway mucosal oedema, leading to symptomatic improvement, improved pulmonary function and shorter hospital admissions.

Competing interests

None declared.

References

1. Totapally BR, Demerici C, Zureikat G, Nolan B: **Tidal breathing flow-volume (TBFV) loops in bronchiolitis in infancy: the effect of albuterol [ISRCTN47364493].** *Crit Care* 2002, **6**:160-165.
2. Dobson JV, Stephens-Groff SM, McMahon SR, Stemmler MM, Brallier SL, Bay C: **The use of albuterol in hospitalized infants with bronchiolitis.** *Pediatrics* 1998, **101**:361-368.
3. Can D, Inan G, Yendur G, Oral R, Gunay I: **Salbutamol or mist in acute bronchiolitis.** *Acta Paediatr Jpn* 1998, **40**:252-255.
4. Cengizlier R, Saraclar Y, Adalioglu G, Tuncer A: **Effect of oral and inhaled salbutamol in infants with bronchiolitis.** *Acta Paediatr Jpn* 1997, **39**:61-63.
5. Goh A, Chay OM, Foo AL, Ong EK: **Efficiency of bronchodilators in the treatment of bronchiolitis.** *Singapore Med J* 1997, **38**:326-328.
6. Chowdhury D, al Howasi M, Khalil M, al Frayh AS, Chowdhury S, Ramia S: **The role of bronchodilators in the management of bronchiolitis: a clinical trial.** *Ann Trop Paediatr* 1995, **15**:77-84.
7. Reijonen T, Korppi M, Pitkakangas S, Tenhola S, Remes K: **The clinical efficiency of nebulized racemic epinephrine and albuterol in acute bronchiolitis.** *Arch Pediatr Adolesc Med* 1995, **149**:686-692.

8. Gadomski AM, Lichenstein R, Horton L, King J, Keane V, Permutt T: **Efficiency of albuterol in the management of bronchiolitis.** *Pediatrics* 1994, **93**:907-912.
9. Wang EE, Milner R, Allen U, Maj H: **Bronchodilators for the treatment of mild bronchiolitis: a factorial randomized trial.** *Arch Dis Childh* 1992, **67**:289-293.
10. Sly PD, Lanteri CJ, Raven JM: **Do wheezy infants recovering from bronchiolitis respond to inhaled salbutamol?** *Pediatr Pulmonol* 1991, **10**:36-39.
11. Klassen TP, Rowe PC, Sutcliffe T, Ropp LJ, McDowell IW, Li MM: **Randomized trial of salbutamol in acute bronchiolitis.** *J Pediatr* 1991, **118**:807-811.
12. Schuh S, Canny G, Reisman J, Kerem E, Bentur L, Petric M, Levison H: **Nebulized albuterol in acute bronchiolitis.** *J Pediatr* 1990, **117**:633-637.
13. Schuh S, Johnson D, Canny G, Reisman J, Shields M, Kovesi T, Kerem E, Bentur L, Levison H, Jaffe D: **Efficacy of adding nebulized ipratropium bromide to nebulized albuterol therapy in acute bronchiolitis.** *Pediatrics* 1992, 90:920-923.
14. Menon K, Sutcliffe T, Klassen TP: **A randomized trial comparing the efficacy of epinephrine with salbutamol in the treatment of acute bronchiolitis.** *J Pediatr* 1995, **126**:1004-1007.
15. Bertrand P, Aranibar H, Castro E, Sanchez I: **Efficiency of nebulized epinephrine versus salbutamol in hospitalized infants with bronchiolitis.** *Pediatr Pulmonol* 2001, **31**:284-288.
16. Sanchez I, De Koster J, Powell RE, Wolstein R, Chernick V: **Effect of racemic epinephrine and salbutamol on clinical score and pulmonary mechanics in infants with bronchiolitis.** *J Pediatr* 1993, **122**:145-151.
17. Kristjansson S, Loprup-Carlsen KC, Wennergren G, Strannegard IL, Carlsen KH: **Nebulised racemic adrenaline in the treatment of acute bronchiolitis in infants and toddlers.** *Arch Dis Childh* 1993, **69**:650-654.
18. Barr FE, Patel NR, Newth CJ: **The pharmacologic mechanism by which inhaled epinephrine reduces airway obstruction in respiratory syncytial virus-associated bronchiolitis.** *J Pediatr* 2000, **136**:699-700.
19. Mikkilineni S, England S: **On tidal expiratory flow measurements in infants.** *Pediatr Pulmonol* 1994, **18**:71-72.
20. van der Ent CK, van der Grinten CP, Meessen NE, Luijendijk SC, Mulder PG, Bogaard JM: **Time to peak tidal expiratory flow and neuromuscular control of expiration.** *Eur Resp J* 1998, **12**:646-652.
21. Main E, Castle R, Stocks J, James I, Hatch D: **The influence of endotracheal tube leak on the assessment of respiratory function in ventilated children.** *Intens Care Med* 2001, **27**: 1788-1797.