Randomised controlled trial of a combination of Dexamethasone and Adrenaline for Bronchiolitis (DAB Trial)

Background

Bronchiolitis is an acute infection of the lower respiratory tract, characterised by rhinorrhea, cough, wheezing, respiratory distress and hypoxemia (Turner 2008; Chang 2009). Many viruses cause this collection of signs and symptoms. The most common causative organism is respiratory syncytial virus (RSV), however parainfluenza, adenovirus and influenza can also result in bronchiolitis. Bronchiolitis is the leading cause of hospitalisation during the first year of life; it accounts for 21% of all hospital admissions in children under 1 year of age, and is a major cause of morbidity and mortality in children (Shay 1999; Leader 2003; Bush 2007). Victorian state-wide data for the calendar year 2006 revealed 2280 admissions for bronchiolitis, with an average length of stay of 3.2 days, with 186 (7.4%) patients admitted to intensive care (Oakley 2010). The estimated cost of the Victorian bronchiolitis hospital admissions for 2006 was $8.1 million (Oakley 2010). In the United States, annual hospital costs for RSV-associated bronchiolitis were estimated at $365 million to $691 million in 1998 (Shay 1999). Currently at the RCH over 1500 children present to the Emergency Department every year with bronchiolitis, with approximately 500 patients admitted to hospital and 100 admitted to the Paediatric Intensive Care Unit (PICU).

The treatment of bronchiolitis is controversial. Many studies have looked at possible treatments for bronchiolitis, with the most commonly investigated being bronchodilators, adrenaline and corticosteroids. Few treatments have demonstrated any clinical benefit to patients (Wainwright 2003; Corneli 2007; Somers 2009; Gadomski 2010; Spurling 2010), and several bronchiolitis treatment guidelines recommend no pharmacological treatments at all (Turner 2008; Petruzella 2010). Despite this lack of evidence, patients continue to be treated with a range of interventions including oxygen, adrenaline. bronchodilators, antibiotics and corticosteroids with evidence to suggest that treatment is given independent of the severity of the illness (Plint 2004; De Brasi 2010). Given the vulnerable population that presents with bronchiolitis it is important that practice is based on sound evidence.

Recently, a large multicentre trial was completed which demonstrated a significant benefit for children presenting to the emergency department (ED) with bronchiolitis. The trial was conducted by the Canadian Pediatric Emergency Research Group (PERC), and showed a significant reduction in hospital admissions in children who presented to ED with bronchiolitis if they were treated with nebulised adrenaline in combination with oral dexamethasone compared to placebo over a 6 day period (Plint 2009). The sickest patients, and those at high risk of severe illness, such as <37 weeks gestation and chronic cardiopulmonary disease, were excluded from the study. Consequently, it is difficult to extrapolate this result to the treatment of bronchiolitis patients who are admitted to intensive care Unit. Therefore, a further study is necessary to determine whether treatment with dexamethasone and adrenaline benefits children with severe bronchiolitis.

Aims

The aim of this study is to determine if the combination of parenteral dexamethasone and nebulised adrenaline will decrease the length of positive pressure ventilation in children admitted to the PICU with a diagnosis of bronchiolitis.

Study Design

The study is a randomised controlled trial in infants less than 18 months of age diagnosed with bronchiolitis who require admission to the PICU or Neonatal Intensive Care Unit (NICU). A combined treatment of parenteral dexamethasone and nebulised adrenaline will be compared to standard treatment with length of positive pressure ventilation in the first 5 days of admission being the primary endpoint.

Prior to randomisation, patients will be stratified by (i) unit, (ii) level of respiratory support (none, non-invasive positive pressure, endotracheal intubation and mechanical ventilation) at the time of randomisation, and (iii) the presence of a risk factor (either cyanotic congenital heart disease or chronic lung disease requiring oxygen therapy for more than 14 days in the last 6 months).

Once recruited and randomised, patients will be given either a combination of corticosteroids and nebulised adrenaline, or standard therapy (Diagram 1). Patients in the treatment group will receive 0.6 mg/kg dexamethasone IM or IV as a loading dose, then 1 mg/kg of methylprednisolone IV or prednisolone NG or orally 8 hourly for 9 doses. Starting with the loading dose of dexamethasone, patients will be given 5 doses of adrenaline 0.05ml/kg of 1% adrenaline (or 0.5ml/kg of 1/1000 adrenaline) made up to 6ml with 0.9% saline

and nebulised using 10L/min of 0_2 and repeated every 30 minutes to a total of 5 doses, then given 1-4 hourly, depending on the patient response, for up to 72 hours providing the resting heart rate is <180.

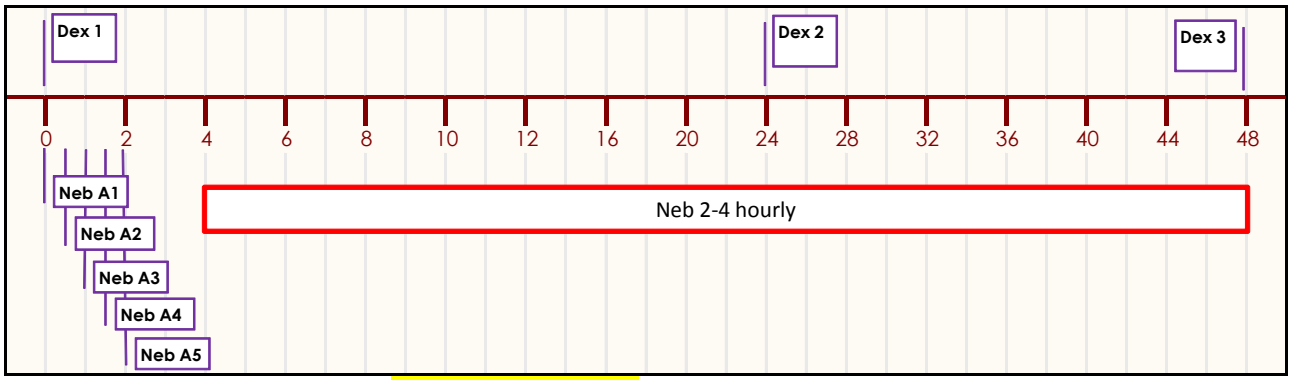

Diagram 1. Treatment Timeline (needs to be changed)

X-axis- hours; purple boxes- protocolised doses, red boxes- clinically indicated doses. Neb- nebulised adrenaline, dex- dexamethasone

If the child is becoming exhausted or has SpO2 <92% despite oxygen, give nasopharyngeal CPAP (NCPAP) of 6-12 cm H2O (Beasley, BMJ 1981;283:1506-8). If the child is becoming tired or has SpO2 <92% despite NCPAP, consider endotracheal intubation and mechanical ventilation using pressure support.

Outcome Measures

Primary

Duration of positive pressure support required from the time of admission to the study until five days (120hrs) after admission.

Secondary

1. PICU/NICU and hospital length of stay
2. Rate of intubation
3. Duration of intubation

Inclusion and Exclusion criteria

This study will be conducted at 3 specialist PICUs in Australia and New Zealand and one NICU in Australia. Patients will be enrolled if they meet all the following criteria:

Inclusion

- a clinical diagnosis of bronchiolitis, defined as a first or second episode of wheezing or respiratory distress associated with a respiratory tract infection
- less than 18 months of age
- no previous admission to this study
- admission to a PICU or NICU involved in the study
- recruitment and initiation of the study therapy within 1hr of admission to PICU or NICU

Exclusion

- on immunosuppressive treatment, including any dose of corticosteroids in the last 7 days

Sample size considerations and timeline

We studied 1723 children with bronchiolitis admitted to PICUs in Australia and New Zealand in the four years 2001-2004; 1096 children received respiratory support, and the mean of the natural log of the hours of respiratory support was 4.08 (geometric mean 59.4 hours), with a SD of 1.10. Consequently, to detect a reduction of 24hrs or more in the duration of respiratory support with a power of 90% and a p-value of 0.05, 87 ventilated patients will be needed in the treatment group and 87 in the control group. As only 63.6% of the children admitted to ICU received respiratory support in 2001-2004, 137 children will need to be randomised to the treatment group and 137 to the control group.

Timeline

Natural fluctuations in the yearly severity of the RSV outbreak causes variation in the number of bronchiolitis admissions from year to year. Nevertheless, admission data from 2009 and 2010 suggests that there will be a total of 100-150 patients eligible for recruitment each year at the four centres. Past experience suggests that approximately 50% of those eligible are likely to be enrolled, resulting in 50-75 patients every year. With these numbers, the study will take approximately 4-5 years to complete. Recruitment is aimed to start at the beginning of the 'bronchiolitis season' in March 2012 and continue until March 2016-2017.

Randomisation

After consent has been obtained, randomisation will be performed online by the European Academic Trials Data Centres Service (TENALEA). This system was used previously for the trail of aminophylline for bronchiolitis, in which two of the four centres participated. Patients will be stratified by ICU, the level of ventilatory support at the time of randomisation, and by presence of risk factors for increased severity of illness.

Run In Phase and Compliance with Study Procedures

The first two patients at each centre will be used as the run-in patients and will follow the trial protocol including randomisation. All case report forms (CRFs) will be completed within two weeks of discharge from the PICU/NICU and the data will be reviewed by the study co-ordinating centre within two weeks of the receipt of data. This audit will document the feasibility of the trial and the adherence to the management strategies proposed, and the Chief Investigator will contact the site investigator to discuss any deviations.

Data Collection and Analysis

Screening Log. All screened patients will be given an identifiable study code and entered in to a screening log. Children who meet criteria for the study and are not randomised will have the reasons for not being randomised recorded, and will have a limited set of data collected.
Data Collection. Data will be collected using the TENALEA eCRF system, which can be accessed using a standard internet browser on any computer. The system is validated, has been certified by registered auditors and is compliant with relevant regulations such as the FDA's CRF 21 Part 11. Intensive care unit data will be collected for 5 days after recruitment.
Adverse Events. The RCH Ethics Committee and the Chief Investigator will be notified within 24 hours of any serious adverse event. Serious adverse events are defined as any event which causes death, is life threatening or results in a persistent significant disability.
Data Analysis. Data analysis will be done by an independent statistician in collaboration with the primary investigator. The primary analysis will be performed on all randomised patients according to the intention-to-treat principle.

Outcomes and Significance

The most common reason for non-elective admission to PICU in Australia is viral bronchiolitis, and this imposes a significant financial and time burden on hospitals. Few studies have been able to demonstrate any significant benefit from any treatment among patients with mild to moderate disease. In addition, many of these studies specifically exclude the sickest patients, or those with significant co-morbidities such as prematurity and congenital heart disease. As these patients account for a large proportion of the admissions to intensive care, the efficacy of many bronchiolitis treatments is unknown in the ICU population. Recently, the combination of dexamethasone and adrenaline was demonstrated to reduce admission to hospital in mild to moderately ill patients presenting to the emergency department with a diagnosis of bronchiolitis (Plint 2009). Consequently, it is important that this therapy be evaluated in the highest risk population.

A positive outcome would be an important improvement in the management of severe bronchiolitis, as many current treatments lack credible scientific evidence for their efficacy, but are used because there is a lack of any real alternative (De Brasi 2010). It is difficult to predict the expected savings in healthcare expenditure, as little research has been done on outcome predictions. However, if the hypothesis is proved correct, then there could be a saving of 24 hours of positive pressure ventilation care per patient, saving approximately $1-2 million of Australian health service resources per year.

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