IMMEDIATE OUTCOME OF MECHANICALLY VENTILATED TERM BABIES IN HOSPITAL KOTA BHARU AND HOSPITAL UNIVERSITI SAINS MALAYSIA

by

DR CHE HADIBIAH BT CHE MOHD RAZALI

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ABBREVIATIONS

AS	Apgar score
CI	Confidence interval
cm	Centimeter
DIVC	Disseminated intravascular coagulopathy
g	Gram
HIE	Hypoxic ischemic encephalopathy
HKB	Hospital Kota Bharu
HUSM	Hospital Universiti Sains Malaysia
I: E	Inspiratory to expiratory time ratio
ICH	Intracranial hemorrhage
Kg	Kilogram
LSCS	Lower segment caesarean section
MAS	Meconium aspiration syndrome
MSAF	Meconium stained amniotic fluid
NEC	Necrotizing enterocolitis
NICU	Neonatal Intensive Care Unit
PPHN	Persistent pulmonary hypertension of the newborn
SPSS	Statistical Package for the Social Science
SVD	Spontaneous vertex delivery

ABSTRAK

OBJEKTIF: Mengenalpasti faktor demografi , ciri-ciri klinikal, penyebab serta komplikasi dan faktor-faktor risiko kematian dikalangan bayi yang matang dan mempunyai berat badan ≥ 2.50 Kg yang mendapat bantuan ventilasi.

METODOLOGI: Satu kajian prospektif telah dijalankan dari 1 hb. Julai-31hb.Disember 2000 di Hospital Kota Bharu dan dari 1 hb. Januari-31 hb. Disember 2001 di Hospital Universiti Sains Malaysia .Bayi –bayi yang memenuhi kriteria yand ditetapkan akan dimasukkan kedalam kajian.Segala data-data yang berkaitan seperti faktor demografi, ciri-ciri klinikal, komplikasi dan kematian akan direkodkan. Analisa statistik akan dilakukan bagi mendapatkan faktor-faktor risiko kematian di kalangan bayi-bayi matang yang mendapat bantuan ventilasi.

KEPUTUSAN: Jumlah bayi lelaki yang memerlukan bantuan ventilasi adalah lebih ramai (60.9%) berbanding dengan bayi perempuan (39.1%). Lebih dari 50% bayi yang memerlukan bantuan ventilasi di kalangan golongan kategori berat 3.00-3.49 Kg. Penyebab utama kepada perlunya bantuan ventilasi ini ialah asfiksia (42%), sindrom aspirasi mekonium (28%), radang paru-paru kongenital (21%) dan sepsis (9%). Berbagai komplikasi berlaku kepada bayi-bayi ini termasuk tekanan darah yang rendah,sawan,PPHN dan lain-lain lagi. Faktor risiko yang signifikan dalam menentukan kematian ialah skor Apgar

kurang dari 4 pada 1 minit (p=0.001), pendarahan dalam kepala (p=0.009), PPHN (p=0.018) dan pneumothorax (p=0.036).

KESIMPULAN: Asfiksia,sindrom aspirasi mekonium , radang paru-paru kongenital dan sepsis merupakan penyebab utama kepada bantuan ventilasi dikalangan bayi yang matang . Disamping itu juga, bayi lelaki lebih ramai yang memerlukan bantuan ventilasi. Kedua- dua keputusan ini setanding dengan kajian-kajian yang dibuat di negara lain.Komplikasi yang berlaku dikalangan bayi-bayi ini adalah berkait rapat dengan masalah asfiksia. Pengurangan kadar asfiksia akan dapat mengurangkan kadar bantuan ventilasi dikalangan bayi-bayi yang matang ini.

ABSTRACT

Objectives: To determine the demographic profile, clinical characteristics and common causes of ventilation and complications among ventilated term babies weighing ≥ 2.50 Kg and to determine the predictive factors for the outcome of these ventilated term babies.

Methodology: A prospective study was conducted from 1st July 2000 until 31st December 2000 in Hospital Kota Bharu and from 1st January 2001 to 31st December 2001 in Hospital Universiti Sains Malaysia. All the term babies weighing more than or equal to 2.50 kilogram and received assisted ventilation were included in the study. Data regarding demographic and clinical characteristics were collected and all the complications that occurred during ventilation and the final outcome were documented. The predictors that determine the outcome were analysed using multiple logistic regression.

Results: The proportion of male to female babies that required ventilation were 60.9% and 39.1% respectively and more than 50% of babies weighed between 3.00 –3.49 Kg. The most common reasons for ventilation among term babies were asphyxia (42%), MAS (28%), congenital pneumonia (21%) and sepsis (9%). Many complications occurred while on ventilation like hypotension, seizures, PPHN and others. The significant predictors that determined the outcome of ventilated babies

Were Apgar score less than 4 at 1minute (p=0.001), intracranial haemorrhage (p=0.009), PPHN (p= 0.018) and pneumothorax (p=0.036).

Conclusions: Asphyxia, MAS, congenital pneumonia and sepsis were the most common cause of ventilation and assisted ventilation was common among male babies. These results corresponded well to other studies. The complications that occured were mostly related to asphyxia and most causes of death were preventable.

INTRODUCTION

The outcome of preterm babies has been well documented and described but not the "bigger" size babies. These bigger size term babies were considered low risk babies but if they require admission to the neonatal intensive care unit, they must be managed aggressively. It is important to identify those at risk among them, so that we can anticipate the problems that might occur in high risk cases and prevent further complications. However not many studies were conducted looking at this problem specifically among those that received artificial ventilation. In view of these discrepancies in the documented data concerning term babies who required ventilatory support, we conducted this study to look at the clinical characteristics, outcome and predictors for their outcome.

For all babies, birth weight is determined by two major factors that are duration of gestation and intrauterine growth rate. (Kramer, 1987). The lowest risk of neonatal mortality occurs among infants with a birth weight of 3000 to 4000 g whose gestational age is between 38 and 42 weeks. Nevertheless, approximately 40% of all perinatal deaths occur after 37 weeks of gestation in infants weighing 2500 g or more. Many of these deaths occur in the period immediately after birth and are more readily preventable than those of smaller and more immature infants. (Dawodu and Effiong, 1985).

Neonatal care can be categorized into three levels of facilities:

(1) Level I facilities can provide care for normal, healthy newborns with the capacity to stabilize sick infants for transport.

(2) Level II facilities have the capacity for an intermediate level of care of more complicated cases including the administration of intravenous fluids, continuous positive airway pressure , short term ventilation and treatment of pneumothoraces.

(3) Level III facilities contains a neonatal intensive care unit (NICU) capable of complete care of the high risk foetus , neonates and mothers, also have neonatologist and can provide specialized neonatal surgery. (Berg, 1989).

The major determinants of NICU admission among normal birth weight infants include congenital anomalies (21.6%), prematurity despite normal birth weight (22%) and acute complications during the neonatal period. Among those that were admitted, only 59% received active therapy, whereas the remainder received only intensive monitoring. (Gray JE, 1996).

Assisted ventilation is a complex technique that has been responsible for much of the improvement in neonatal morbidity and mortality during the last ten to fifteen years. In unskilled hands, it can be dangerous with complications as high as thirty percent (30%). It requires a constantly available medical and nursing team that can supervise the care of critically ill infants around the clock. (Krauss AN, 1980).

A certain number of infants were able to survive without assisted ventilation. Therefore, whenever the decision is made to begin assisted ventilation, the risk must be carefully weighed against the benefits to be gained. Sometimes the decision to begin assisted ventilation cannot be based on blood gases that are abnormal. (Krauss AN, 1980).

The main function of assisted ventilation is to treat the respiratory failure. In any patients, regardless of age, the respiratory failure can take two forms. In one form, the infants are apnoeic and assisted ventilation is undertaken simply because the infants cannot breathe without assistance and lungs are often normal. The second group of infants requiring ventilation is those in whom failure of the pulmonary exchanges mechanism has occurred. The infants manifest as hypoxemia, hypercapnea and respiratory failure. (Kraus AN, 1980)

Assisted ventilation consists of supplying an additional volume of air to the lungs during a given period of time sufficient to remove the carbon dioxide that is produced by the metabolic process during that particular interval and to supply the oxygen needed in order to allow these metabolic processes to continue without excessive production of lactic acids. (Kraus AN 1980).

The earliest manifestation of impaired respiratory function is often hypoxemia (partial pressure oxygen < 50mmHg) which is usually managed by the addition of

supplemental oxygen alone to ambient air. If hypoxemia progresses or respiratory acidosis developes, artificial ventilation with a mechanical ventilator should be initiated. (Kraus AN 1980).

In infants who had meconium aspiration syndrome, they were prone to develop respiratory failure that can be recognized based on these parameters; partial pressure oxygen (PaO2) less than 50mmHg in fraction inspired oxygen (fiO2) 1.00, partial pressure carbon dioxide (PaCO2) more than 75mmHg or recurrent apnoea. During the period of assisted ventilation, an attempt was made to keep partial pressure oxygen (PaO2) between 50-90 mmHg and partial pressure carbon dioxide (PaCO2) less than 65 mmHg. (Vidyasagar, 1975).

The infant will be weaned down from the respirator once the clinical and biochemical parameters were permissible, since ventilation is a known risk for infection. Apart from that, its complications can compromise systemic circulation in several ways. (Srimarthi G, 2000).

1. **Causes of ventilation**

Preterm infants with respiratory distress syndrome or term infants with various causes usually require assisted ventilation

1.1 Perinatal asphyxia

Throughout the world, perinatal asphyxia remains an important cause of perinatal acquired brain injury in full term infants and produces a huge burden of worldwide disability. The incidence of death or severe neurological impairment following perinatal asphyxia is 0.5 to 1.0 per 1000 live births in developed countries. (Finer, 1981).

Mac Donald (1980) reported that the incidence of asphyxia was indirectly related to the gestational age and weight. It was as low as 0.4% in infants > 38 weeks and increased up to 62.3% in infants < 27 weeks. Concerning birth weight, the incidence was 0.5% and 72.3% in infants >2500 gram and < 750 gram respectively. Thornberg (1995) stated that the incidence of perinatal asphyxia in Sweden was 2.9 per 1000 live births, but if premature babies were included, the incidence went up as high as 17 per 1000 live births.

In developing countries, perinatal asphyxia appears to be more common. Boo NY et al (1992) reported from their study at Maternity Hospital Kuala Lumpur that the incidence of perinatal asphyxia was 18.7 per 1000 live birth. However, the incidence was significantly more common in the neonates weighing less than 2500g (48.3 per 1000 live births) than those weighing 2500g or more (15.3 per 1000 live births with $p<0.001$). Meanwhile, Al Alfy (1990) from Kuwait reported that the incidence of perinatal asphyxia was 9.4 per 1000 live birth. In Nigeria, the

incidence was higher with value of 26.5 per 1000 live births as stated by Airede (1991). All the above studies using Apgar score as criteria for diagnosing perinatal asphyxia but Boo NY et al also included the intrapartum signs of abnormal foetal heart rate.

The definition of asphyxia is still debatable. Avery (1981) defines asphyxia as a condition that occurs when the organ of gas exchange fails. The failure of the organ of gas exchange, whether it was the lungs or placenta is associated with abnormal blood gas results; that is a rise in partial pressure carbon dioxide (Pa CO2) and a fall in partial pressure oxygen (PaO2), ultimately leading to a decrease in pH value.

The American Academy of Paediatrics (AAP) (1986) suggested that three criterias should be met in order to diagnose asphyxia:

(1) Apgar score of 0-3 at 10 minutes

(2) Early neonatal seizure

(3) Prolonged hypotonia.

The presence of metabolic acidosis in cord blood further helps to confirm suspected hypoxia and multiple organ dysfunctions in the early neonatal period. Jacobs MM (1989) defined asphyxia as combinations of hypoxemia, hypercarbia and metabolic acidosis.

There is no single measurement for consistently qualifying asphyxia. The Apgar score was the first attempt at a systematic assessment. It is useful but has limitations because of maternal anaesthetic, sedatives, maternal drugs, foetal sepsis and central nervous system pathology that can lower down the Apgar score. (American Academy of Paediatrics ,1986).

The scoring of Apgar score should continue every 5 minutes until the score increases to seven or above and the length of time taken to reach a score of seven is a rough sign of severity of asphyxia. (Jacob MM, 1989).

Hypoxic ischemic encephalopathy (HIE) is a clinical syndrome when asphyxia is followed by an abnormal neonatal behaviour. The severity of HIE can be classified to mild, moderate, and severe according to criteria of Sarnat and Sarnat (1976) modified by Fenichel (1983).

(1) Mild HIE is characterized by hyper alertness and irritability, normal muscle tone, normal or hyperactive reflexes, ankle clonus and no seizure.

(2) Moderate HIE includes lethargy, decreased spontaneous movement, proximal muscle weakness, depressed primitive reflexes and seizures.

(3) Severe HIE includes stupor or coma, markedly reduced muscle tone or flaccidity and absent primitive reflexes. Seizures are often frequent and difficult to control but may also be totally absent.

The hypoxic ischemic encephalopathy may result from impaired placental gas exchange or blood flow from umbilical cord compression or may occur postnatally as a result of neonatal respiratory or cardiac compromise. The postnatal insults usually account for only 10% of infants with evidence of hypoxic ischemic encephalopathy. (Finer NN 1981).

The incidence of significant hypoxic ischemic encephalopathy was 3.6/1000 live births and death of 1.3/1000 live birth in term infants. (Finer NN, 1981).

In a study by Finer NN (1981), ninety-five singleton term infants with hypoxic ischemic encephalopathy were studied, 34.7% of them required ventilation with 18.9% had intracranial haemorrhage.

Mildly asphyxiated infant without underlying lung disease would respond quickly to initial lung inflation and will need little or no assisted ventilation or oxygen therapy. This transient post asphyxia event is probably due to ischemic lung injury. (Finer NN, 1981).

There are four potential problems with the systemic circulation in the asphyxiated infant. These occur at different times during the course of resuscitation. There is cardiac arrest or severe myocardial failure at birth, hypovolemic shock, interference with systemic circulation from complication of ventilation and postasphyxial cardiomyopathy. (Jacobs MM ,1989).

An additional important factor in managing asphyxiated infants is hypoglycaemia, which may occur quickly in infants during convalescing period. Repeated screenings of blood glucose will detect this condition. Therefore, it is important to check the blood sugar as soon as the initial resuscitation measures are completed. (Jacob MM, 1989).

1.2 Meconium aspiration syndrome (MAS)

Meconium is a viscous green liquid that consists of gastrointestinal tract secretions: bile, bile acids, mucus, pancreatic juice, cellular debris, amniotic fluid, swallowed vernix, lanugo and blood. It's present in the foetal gastrointestinal tract starting from the 10^{th} to 16^{th} week of gestation. (Holtzman et al, 1989).

Initially, the passage of meconium in utero was thought to be solely related to foetal asphyxia. However, many studies done have failed to show a consistent effect of asphyxia on the intrauterine passage of meconium. (Katz and Bowes, 1992).The intrauterine passage of meconium is not only thought to be related to asphyxia alone, but also the result of physiological gastrointestinal maturity.

The passage of meconium in most cases is probably a physiological event related to increasing maturity of the foetus; however, it is possible that it will at times occur as the result of foetal hypoxia and acidosis. (Miller FC 1975). It is probable that

whenever meconium happens to be present in the amniotic fluids, foetal hypoxemia plus acidosis can result in gasping and consequent in utero aspiration of meconium. (Miller, 1975, Block, 1981).

The passage of meconium by the foetus is believed to be a maturational event. In a study by Matthews and Warshaw (1979) the majority of meconium staining of the amniotic fluid (MSAF) occurred in term newborns (98.4%) and none in those less than 34 weeks of gestation. Myelination of the neural plexus of the gastrointestinal tract progresses throughout gestation and as the nervous system continues to mature in utero, parasympathetic stimuli are propagated to initiate defecation, thus resulting in intrauterine passage of meconium. (Grand RJ, 1976).

The pathophysiology of meconium aspiration syndrome is related to mechanical obstruction of the airway and inactivation of the surfactant system by the meconium leading to pulmonary atelectasis .This is followed by the development of chemical pneumonitis that contributes to further pulmonary damage. (Lam BCC, 1999).

Meconium staining of amniotic fluid occurred in between 9 to 14 percent of all pregnancies at the time of delivery. Indeed, the incidence can be as high as 44 percent in post date pregnancies. (Knox GE, 1979). Meconium aspiration syndrome is a severe respiratory illness affecting mostly full term babies and often requiring assisted ventilation and oxygen. (Swaminathan, 1989).

line results in increased activation of the transcription factor NF-B, with consequent increased release of interleukin-8 in response to endotoxin and increased expression of intercellular adhesion molecule 1, providing a molecular mechanism for the amplification during the inflammatory response (54).

Although smoking is the principal cause of COPD, quitting smoking does not appear to result in resolution of the inflammatory response in the airways (55,56). This suggests that there are perpetuating mechanisms that maintain the chronic inflammatory process once it has become established. Such mechanisms may account for the presentation of COPD in patients who have stopped smoking many years before their first symptoms develop. The mechanisms of disease persistence are currently unknown.

f) Acute Exacerbations

Although acute exacerbations of COPD as defined by increased symptoms and worsening lung function are a common cause of hospital admission, their mechanism is far from clear. Acute exacerbations may be prolonged and may have a profound effect on the quality of life (57). It was always assumed that the increased amount and purulence sputum were due to bacterial infection of the respiratory tract. It is now evident that many exacerbations in COPD, as in asthma, are due to upper respiratory tract viral infections (such as rhinovirus infection) and to environmental factors, such as air pollution and temperature (58,59). There is an increase in neutrophils and in the concentrations of interleukin-6 and interleukin-8 in sputum during an exacerbation, and patients who have frequent exacerbations have higher levels of interleukin-6, even when COPD is stable

(60). Bronchial biopsies show an increase in eosinophils during exacerbations in patients with mild COPD (24) but there is no increase in sputum eosinophils during exacerbations in patients with severe COPD (60). An increase in markers of oxidative stress and exhaled nitric oxide, presumably reflecting increased airway inflammation, is observed during exacerbations (39,61,62).

g) Treatment of COPD

Smoking cessation is the only measure that will slow the progression of COPD, as confirmed in the large Lung Health Study (63). Nicotine-replacement therapy (by gum, transdermal patch, or inhaler) provides help to patients in quitting smoking (64) but the use of the recently introduced drug bupropion, a noradrenergic antidepressant, has proved to be the most effective strategy to date. A recent controlled trial showed that after a 9-week course of bupropion, abstinence rates were 30 percent at 12 months, as compared with only 15 percent with placebo. The abstinence rate was slightly improved with the addition of a nicotine patch (65).

Bronchodilators are the mainstay of current drug therapy for COPD. Bronchodilators cause only a small (<10 percent) increase in FEV_1 in patients with COPD, but these drugs may improve symptoms by reducing hyperinflation and thus dyspnoea, and they may improve exercise tolerance, despite the fact that there is little improvement in spirometric measurements (66). Several studies have demonstrated the usefulness of the long-acting inhaled $ß_2$-agonists salmeterol and formoterol in COPD (67,68,69). An additional benefit

of long-acting $ß_2$-agonists in COPD may be a reduction in infective exacerbations, since these drugs reduce the adhesion of bacteria such as *Haemophilus influenzae* to airway epithelial cells (70).

COPD appears to be more effectively treated by anticholinergic drugs than by $ß_2$-agonists, in sharp contrast to asthma, for which $ß_2$-agonists are more effective (71). A new anticholinergic drug, tiotropium bromide, which is not yet available for prescription, has a prolonged duration of action and is suitable for once-daily inhalation in COPD (72).

Acute exacerbations of COPD are commonly assumed to be due to bacterial infection, since they may be associated with increased volume and purulence of the sputum. However, as noted above, it is increasingly recognized that exacerbations may be due to viral infections of the upper respiratory tract or may be noninfective (58) so that antibiotic treatment is not always warranted. A meta-analysis of controlled trials of antibiotics in COPD showed a statistically significant but small benefit of antibiotics in terms of clinical outcome and lung function (73). Although antibiotics are still widely used for exacerbations of COPD, methods to diagnose bacterial infection reliably in the respiratory tract are needed so that antibiotics are not used inappropriately. There is no evidence that prophylactic antibiotics prevent acute exacerbations.

Inhaled corticosteroids are now the mainstay of therapy for chronic asthma, and the recognition that chronic inflammation is also present in COPD provided a rationale for their use in COPD. Indeed, inhaled corticosteroids are now widely prescribed for COPD,

and in North America they are used as frequently in patients with COPD as in those with asthma. However, the inflammation in COPD is not suppressed by inhaled or oral corticosteroids, even at high doses (34,77). This lack of effect may be due to the fact that corticosteroids prolong the survival of neutrophils (78) and do not suppress neutrophilic inflammation in COPD.

Approximately 10 percent of patients with stable COPD have some symptomatic and objective improvement with oral corticosteroids (102). It is likely that these patients have concomitant asthma, since both diseases are very common. Indeed, airway hyper-responsiveness, a characteristic of asthma, may predict an accelerated decline in FEV_1 in patients with COPD (14). Recent studies had found no evidence that long-term treatment with high doses of inhaled corticosteroids reduced the progression of COPD, even when treatment was started before the disease became symptomatic.

Home oxygen therapy accounts for a large proportion of the costs of treating COPD (over 30 percent in the United States, where expensive liquid oxygen is widely used). Long-term oxygen therapy was justified by two large trials that showed reduced mortality and improvement in quality of life in patients with severe COPD and chronic hypoxemia (partial pressure of arterial oxygen, <55 mm Hg) (74). More recent studies have demonstrated that oxygen does not increase survival in patients with less severe hypoxemia, so that the selection of patients is important in prescribing this expensive therapy (75). Similarly, in patients with COPD who have nocturnal hypoxemia, nocturnal

treatment with oxygen does not appear to increase survival or delay the prescription of continuous oxygen therapy (76).

Inhaled corticosteroids may slightly reduce the severity of acute exacerbations (83) but it is unlikely that their use can be justified in view of the risk of systemic side effects in these susceptible patients and the expense of using high-dose inhaled corticosteroids for several years.

By contrast, two recent studies have demonstrated a beneficial effect of systemic corticosteroids in treating acute exacerbations of COPD, with improved clinical outcome and reduced length of hospitalization (84,85). The reasons for this discrepancy between the responses to corticosteroids in acute and chronic COPD may be related to differences in the inflammatory response (such as increased numbers of eosinophils) or airway oedema in exacerbations.

h) Nonpharmacologic Treatments

Noninvasive Ventilation

The use of noninvasive positive-pressure ventilation with a simple nasal mask, which eliminates the necessity for endotracheal intubation, reduces the need for mechanical ventilation in acute exacerbations of COPD in the hospital (86) although some studies have shown little or no benefit (87). Uncontrolled studies have shown that noninvasive

positive-pressure ventilation used at home may improve oxygenation and reduce hospital admissions in patients with severe COPD and hypercapnoea and may improve long-term survival, although large, controlled trials are now needed (88). In one small, controlled trial, noninvasive positive-pressure ventilation was not well tolerated and produced only marginal benefits (89). The combination of noninvasive positive-pressure ventilation and long-term oxygen therapy may be more effective (90) but larger trials are needed before this combined therapy can be routinely recommended.

Pulmonary Rehabilitation

Pulmonary rehabilitation consisting of a structured program of education, exercise, and physiotherapy has been shown in controlled trials to improve exercise capacity and quality of life among patients with severe COPD (91) and to reduce the amount of health care needed (92).

Lung-Volume–Reduction Surgery

There has been considerable interest in the surgical removal of the most emphysematous parts of the lung to improve ventilatory function (93,94). The reduction in hyperinflation improves the mechanical efficiency of the inspiratory muscles. Careful selection of patients after a period of pulmonary rehabilitation is essential. Patients with localized upper-lobe emphysema appear to do best; relatively low lung resistance during inspiration appears to be a good predictor of improved FEV_1 after surgery (95). Functional

improvements include increased FEV_1, reduced total lung capacity and functional residual capacity, improved function of respiratory muscles, improved exercise capacity, and improved quality of life (96,97). The benefits persist for at least a year in most patients, but careful extended follow-up is needed to evaluate the long-term benefits of this therapy. A large, multicenter study, the National Emphysema Treatment Trial, is now under way in the United States to investigate the effectiveness and cost of lung-volume–reduction surgery in comparison with conventional therapy (98).

Randomised trials had been published on the efficacy of systemic corticosteroid treatment in acute exacerbation of COPD using treatment that differed in initial dose (prednisolone 30mg/day, prednisone 60mg/day, hydrocortisone 600mg/day; methylprednisolone 2mg/kg/day to 500mg/day) and duration (3 to 56 days)(84,85,101,103,104). It is difficult to draw any conclusion from these data as to the optimal dose and treatment duration of systemic steroid used in COPD exacerbations. This study was undertaken to look at the effectiveness of oral prednisolone 20mg daily for two weeks in acute exacerbation of COPD.

Objective

The main objective of this study is to evaluate the effectiveness of oral corticosteroid as a treatment for acute exacerbation of chronic obstructive pulmonary disease (COPD)

Hypothesis

Oral corticosteroid is superior than placebo in improving airway obstruction in patients presenting with acute exacerbation of COPD

Methodology and Subjects

Settings in this study

Patients with the diagnosis of COPD presenting with acute exacerbation to casualty or outpatient department in Hospital Alor Setar from 1st August 1999 to 1st April 2000 were selected. Acute exacerbation was defined as increasing breathlessness and at least 2 of the following symptoms:

1. increased cough frequency or severity
2. increased sputum volume or purulence
3. increased wheeze

Inclusion criteria were

Patients with

- acute exacerbation of COPD
- age 40 to 80 years
- smoking history of at least 20 pack-years

Exclusion criteria

The following patients were excluded from the study

- History of asthma or atopy
- Left ventricular failure
- Clinical or radiological evidence of pneumonia
- Had received oral corticosteroid within one month of presentation
- Arterial blood pH less than 7.30

Study Design

Full medical history and physical examination were taken on admission. Blood sample was also taken for arterial blood gases. Sputum was collected for acid-fast bacilli direct smear and also for culture and sensitivity.

Eligible patients received standard treatment with nebulised B_2 agonist (5 mg Salbutamol) and an anticholinergic (500 ug ipratropium bromide) every 6 hours and controlled oxygen therapy. Any patient who was receiving inhaled corticosteroid before randomization was continued on this therapy.

Patients were randomised to receive prednisolone 20 mg everyday or similar-appearing placebo (Vitamin B6) for two weeks. This particular dose of prednisolone was chosen because of the relatively smaller size of our local population as compared to western population. One study done in the United Kingdom for acute exacerbation of COPD used 30 mg of prednisolone to compare with placebo(85).

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Randomisation was done by hospital pharmacy. The medication pack supplied by the pharmacy were labeled A and B.

Spirometry was done daily before and 15 minutes after 5 mg nebulised salbutamol. A daily symptom score was obtained, calculated from a questionnaire completed by the patient. Questions were asked about breathlessness, sputum production, wheeze, mobility, sleep quality, cough and general well being. Patients were asked to score each of the symptoms from 0 (more than usual) to 5 (much worse than usual). The questionnaire was piloted earlier among fifty patients admitted in medical ward.

Data were also collected about potential side effects of oral corticosteroids (mood swings, heart burn and overt gastrointestinal bleeding). Patients' urine was tested daily for glucose. Daily morning capillary blood sugar was also done.

Study duration was from the time of admission to the time of discharge and included a follow-up visit six weeks after admission.

The physician in charge of the patients were free to withdraw patients from this study at any time if they felt clinical improvements were not satisfactory. Patients were also free to withdraw at any time if they were not satisfied with their progress.

The physician incharge also decided the time at which patients were medically fit for discharge. The patients were instructed to complete their treatment after discharge and to bring their treatment pack during follow-up.

Six weeks after starting treatment, patients were recalled to repeat spirometry before and after 5 mg nebulised salbutamol. Their medication pack was checked to make sure the treatment was completed after discharge.

Statistical Analysis

We calculated (two means) that a sample size of 24 in each group would give us 80% power to detect a difference of 0.05L per day in mean FEV_1 between the two groups, with a standard deviation of 0.0625.

We calculated means (standard error) and used Student's *t* test to compare normally distributed data. We used χ^2 test to compare proportions.

Ethical Clearance

This study protocol was approved by local ethical committee in Hospital Alor Setar

Results

A total of seventy five patients were screened and admitted in Hospital Alor Setar during the study. Sixty two patients met the inclusion criteria. Reasons for exclusion included the use of oral corticosteroid in the past four weeks, evidence of pneumonia and pulmonary tuberculosis. Two patients were confirmed to have pulmonary tuberculosis. (Figure I)

Nine patients refused to sign consent of which three of them refused oral corticosteroid after being told of the possible side effects. Six patients did not wish to participate in the trial.

Twenty seven patients were randomly assigned to active treatment and twenty six were assigned to placebo. Four patients were withdrawn from the study; two in the corticosteroid group (day four and day five) and two in the placebo group (day three and day five). Two patients in the corticosteroid group had severe gastrointestinal upset. However, oesophagogastroduodenoscopy which was done for both patients were normal. One patient in the placebo group died due to acute extensive myocardial infarction. The other patient had asked to be withdrawn because he didn't feel better after treatment in the ward.

Figure I : Trial Profile