Partial liquid ventilation for the prevention of mortality and morbidity in paediatric acute lung injury and acute respiratory distress syndrome (Review)

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ABSTRACT

Background
Acute lung injury , and acute respiratory distress syndrome , are syndromes of severe respiratory failure. Children with acute lung injury or acute respiratory syndrome have high mortality and significant morbidity. Partial liquid ventilation is proposed as a less injurious form of respiratory support for these children. Uncontrolled studies in adults have shown improvement in gas exchange and lung compliance with partial liquid ventilation A single uncontrolled study in six children with acute respiratory syndrome showed some improvement in gas exchange during three hours of partial liquid ventilation.

Objectives
To assess whether partial liquid ventilation reduces either mortality or morbidity, or both, in children with acute lung injury or acute respiratory syndrome .

Search strategy
We searched The Cochrane Central Register of Controlled Trials (CENTRAL), *The Cochrane Library* issue 2, 2003; MEDLINE (1966 to April 2003); and CINAHL (1982 to April 2003); intensive care journals and conference proceedings; reference lists and 'grey literature'.

Selection criteria
Randomized controlled trials which compared partial liquid ventilation with other forms of ventilation, in children (28 days - 18 years) with acute lung injury or acute respiratory syndrome, reporting one or more of the following: mortality; duration of mechanical ventilation, respiratory support, oxygen therapy, stay in the intensive care unit, or stay in hospital; infection; or long term cognitive impairment or neurodevelopmental progress or other long term morbidities.

Data collection and analysis
Two reviewers independently evaluated the quality of the relevant studies and extracted the data from the included studies.

Main results
Only one study enrolling 182 patients (only reported as an abstract in conference proceedings) was identified and found eligible for inclusion: the authors report only limited results. The trial was stopped prematurely and therefore under-powered to detect any significant differences. The only outcome of clinical significance available was 28 day mortality: there was no statistically significant difference between groups with a relative risk for 28 day mortality in the partial liquid ventilation group of 1.54 (95% confidence intervals of 0.82 to 2.9).

Authors' conclusions
There is no evidence from randomized controlled trials to support or refute the use of partial liquid ventilation in children with acute lung injury or acute respiratory syndrome: adequately powered, high quality randomized controlled trials are still needed to assess its

efficacy. Clinically relevant outcome measures should be assessed (mortality at discharge and later, duration of respiratory support and hospital stay, and long-term neurodevelopmental outcomes) and the studies should be published in full.

PLAIN LANGUAGE SUMMARY

There is no evidence from randomized controlled trials (RCT) to support or refute the use of partial liquid ventilation in children with severe lung disease.

Severely ill children can get severe lung disease that stops enough oxygen getting into the blood - this is called acute lung injury or acute respiratory distress syndrome. About half of these children die. To improve the supply of oxygen to the body and prevent further injury to the lung, a special liquid (perfluorocarbon liquid) is introduced into the lungs to partly replace the gas in normally gas-filled lungs. This is called partial liquid ventilation (PLV). Only one poorly reported trial has been done on PLV in children and this does not provide enough evidence to support its use.

BACKGROUND

Acute lung injury (ALI), known in its most severe form as acute respiratory distress syndrome (ARDS), is a syndrome of severe respiratory failure characterized by acute onset, severe hypoxaemia and bilateral chest infiltrates on chest x-ray, without evidence of left heart failure. ARDS was first described by Ashbaugh in 1967 (Ashbaugh 1967) in a case series that included one 11 year old child. The causes of ALI or ARDS are many and they may result from primary lung disease (pneumonia, aspiration or inhalation injury, lung trauma, fat emboli, near-drowning) or extrapulmonary causes (septicaemia, trauma and shock, cardio-pulmonary bypass, drug overdose, acute pancreatitis, transfusion) (Ware 2000). Malignancy and infection (septicaemia or pneumonia) are common underlying antecedents in children (Timmons 1991; DeBruin 1992; Davis 1993).

ALI or ARDS results in poor matching of ventilation and perfusion within the lung, and subsequent severe hypoxaemia. This situation is known as ventilation-perfusion (V/Q) mismatch. They are also characterized by severe heterogeneous atelectasis and decreased lung compliance. Hence, patients with ALI or ARDS universally require respiratory support and the mainstay of treatment is endotracheal intubation and mechanical ventilation (Tobin 2001). The syndromes are also characterized by a prominent pulmonary and systemic inflammatory response. There is loss of integrity of the alveolar-capillary barrier in the lung with increased inflammatory cell and oxygen free radical mediated injury and increased pulmonary and systemic pro-inflammatory cytokines (Ware 2000). ALI or ARDS is further complicated by ventilator-induced lung injury (VILI) and its secondary inflammatory effects. VILI arises through either overdistention of the lung (volutrauma), the use of high pressure within the lung (barotrauma), or a combination of these factors. Decreasing baro- and volu-trauma may lower mortality and morbidity (Tobin 2001; van der Werf 2001).

Generally accepted mortality figures for ALI or ARDS in adults have ranged from 40 to 60% (Ware 2000); although recent studies have shown decreasing mortality over time in adults (Milberg 1995; Abel 1998). Mortality in children seems to be somewhat greater with typical rates higher than 60% (Timmons 1991; DeBruin 1992; Davis 1993; Costil 1995; Paret 1998). Mortality is often due to the primary disease process, especially septicaemia or the associated multiple organ system failure (MOSF), rather than respiratory failure per se (Pfenninger 1996; Monchi 1998; Zilberberg 1998; Ware 2000) and therefore may not be amenable to alterations in ventilatory techniques.

Recent studies show a lower mortality with 'protective' ventilatory strategies and/or an 'open-lung' approach in adults with ARDS. This suggests that VILI does have a role in increasing mortality; and that decreasing baro- and volu-trauma may lead to improved survival (Abel 1998; Amato 1998; ARDS Network 2000; Tobin 2001; Baudouin 2001; van der Werf 2001). A recent Cochrane systematic review (Petrucci 2004) on ventilation with lower tidal volumes versus traditional tidal volumes in adults with ALI or ARDS concluded that whilst short-term mortality was reduced by using ventilation with lower tidal volume there was insufficient evidence to draw any conclusions about morbidity and long term outcomes. Mortality and other outcomes have been shown to vary by the sex and age of the patient, the initial severity of the ALI or ARDS or patients condition and by the underlying cause of the ALI or ARDS (DeBruin 1992; Davis 1993; Monchi 1998; Paret 1998; Ware 2000; Suntharalingam 2001).

There is also substantial short and long term morbidity associated with these syndromes. Short term morbidity leads to prolonged ventilator dependence and prolonged stay in the intensive care unit (ICU) and hospital. Long term morbidity includes decreased lung function, decreased health related quality of life, neuro-developmental delay, cognitive impairments, and high rates of disability (Fanconi 1985; Schelling 2000; Rothenhausler 2001).

The mainstay of treatment of ALI or ARDS is mechanical ventilation. Many forms of additional therapies have been considered and some of these subjected to randomized controlled trials. Adjuncts to mechanical ventilation have included - extracorporeal life support (ECLS), inhaled nitric oxide, endogenous surfactant, prone positioning, high frequency ventilation and a variety of pharmaceutical therapies (anti-inflammatory medication, antioxidants, anticytokine agents, prostaglandins) (Sarnaik 1994; Conner 2000). The ventilatory techniques that seem to improve outcomes in ALI or ARDS are the 'lung-protective' strategies that aim to decrease VILI (Brower 2000; van der Werf 2001).

Partial liquid ventilation (PLV) has been proposed as a less injurious form of respiratory support for patients with severe respiratory failure, ALI and ARDS. In 1991 Fuhrman et al (Fuhrman 1991) introduced the technique of using functional residual capacity (FRC) volumes of perfluorocarbon liquid (PFC) with conventional gas ventilation; they called it perfluorocarbon associated gas exchange (PAGE). This technique has become known as PLV and consists of partially filling the lungs with PFC whilst continuing mechanical ventilation with a gas ventilator. Of the available techniques of liquid assisted ventilation it is PLV which has the most promise for practical clinical application in intensive care. Various models of acute lung injury have shown the benefits of using PLV compared with conventional mechanical ventilation alone. Many animal studies have shown that PLV improves oxygenation, CO_2 removal and lung compliance, and leads to less lung damage and VILI (Davies 1999; Wiedemann 2000). All of these benefits are able to be achieved whilst using lower ventilatory pressures and smaller tidal volumes (Davies 1999; Wiedemann 2000). PLV also gives superior alveolar recruitment in the dependent areas of the lung and redistributes pulmonary blood flow to improve V/Q matching and decrease intra-pulmonary shunting (Davies 1999; Wiedemann 2000). PFCs have also been demonstrated to have significant anti-inflammatory effects in both in vivo animal models of ALI and in vitro cell cultures (Wiedemann 2000). PFCs can decrease inflammatory cytokine release and oxygen free radical production by alveolar macrophages and decrease neutrophil activation and chemotaxis (Wiedemann 2000).

Uncontrolled human studies using PLV in adults with ALI or ARDS have shown improvement in oxygenation and lung compliance in patients also on ECLS (Hirschl 1996), and improved gas exchange with haemodynamic stability and minimal adverse side effects in patients ventilated with PLV alone (Hirschl 1998). The efficacy of PLV in adults with ALI or ARDS is the subject of systematic review currently being prepared (Davies 2003). A single uncontrolled study in six children with ARDS showed some improvement in gas exchange with three hours of PLV (Fedora 1999a). The optimal dose of PFC to use during PLV is unknown and its beneficial effects may be apparent at lower doses of PFC than the usual method where the initial dose of PFC is equivalent to the functional residual capacity (approx. 30 ml/kg). Variations in the technique of PLV may also include giving an initial dose of PFC with or without further top-up doses to maintain partial filling of the lungs (Davies 1999).

OBJECTIVES

The primary objective was to assess whether PLV reduces reduces either mortality or morbidity, or both, in children with ALI or ARDS.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomized, controlled trials (RCTs). Cross-over studies were to be excluded due to their inability to determine differences for clinically relevant medium to long term outcomes.

Types of participants

Children from the age of 28 days to 18 years with ALI or ARDS from any cause who are intubated and are being supported by a mechanical ventilator.

Definition of ALI (Bernard 1994):
1. Acute onset respiratory failure
2. Bilateral opacities on chest x-ray consistent with pulmonary oedema
3. Pulmonary artery wedge pressure less than 18mmHg or no clinical evidence of raised left atrial pressure
4. PaO_2 or FiO_2 ratio less than or equal to 300mmHg.

Definition of ARDS (Bernard 1994):
1. Acute onset respiratory failure
2. Bilateral opacities on chest x-ray consistent with pulmonary oedema
3. Pulmonary artery wedge pressure less than or equal to 18mmHg or no clinical evidence of raised left atrial pressure
4. PaO_2 or FiO_2 ratio less than or equal to 200mmHg.

Types of intervention

Partial liquid ventilation (partially filling the lungs with PFC whilst continuing mechanical ventilation with a gas ventilator) compared with other forms of ventilatory management without the use of perfluorocarbon liquids or vapour.

Types of outcome measures

One or more of the following outcomes must have been reported:
Mortality (28 day, or at discharge from ICU, at discharge from hospital, or at 1, 2, and 5 years)
Duration of mechanical ventilation
Duration of respiratory support
Duration of oxygen therapy
Duration of stay in the intensive care unit

Duration of stay in hospital
Infection (septicaemia, pneumonia)
Long term cognitive impairment
Long term neurodevelopment (cerebral palsy, sensorineural hearing loss, visual impairment and/or developmental delay)
Long term disability
Long term health related quality of life
Long term lung function
Cost

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Anaesthesia Group methods used in reviews.

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), *The Cochrane Library* issue 2, 2003; MEDLINE (from 1966 to April 2003),CINAHL (from 1982 to April 2003), intensive care journals and conference proceedings; reference lists and 'grey literature' for RCTs of PLV in ALI or ARDS.

The MeSH headings and text words applied (MEDLINE) were: MeSH heading :'RESPIRATORY DISTRESS SYNDROME, ADULT' or textwords 'ARDS', 'ALI' or 'acute lung injury' and MeSH heading 'FLUOROCARBONS' or textword 'partial liquid ventilation'. The other databases were searched using a similar strategy.

(Please note: that the MeSH term 'RESPIRATORY DISTRESS SYNDROME, ADULT' is the MeSH term for ALI or ARDS whether it occurs in children or adults.)

- Bibliographies of published trials and conference proceedings, were reviewed.
- We attempted to identify unpublished trials by contacting expert informants in the field of PLV research.
- No language restrictions were applied.

METHODS OF THE REVIEW

The standard methods of the Cochrane Collaboration and its Anaesthesia Review Group were used. The two reviewers worked independently to search for and assess trials for inclusion and methodological quality. Differences were resolved by discussion and consensus of the reviewers.

Studies were assessed using the following key criteria: 1. allocation concealment (blindness of randomization), 2. blindness of intervention, 3. completeness of follow up, and 4. blinding of outcome measurement. Each were rated as either adequate, unclear or inadequate. At least two criteria must have been rated as adequate for the study to be included in the review.

Data were extracted independently by the reviewers. Differences were resolved by discussion and consensus of the reviewers. If necessary, investigators were to be contacted for additional information or data.

For individual trials categorical outcomes, such as mortality, the relative risk and risk difference (and 95% confidence intervals) were reported.

Sub-group analyses were planned to determine whether the results differ by:

Population:
i. age
ii. severity - of a. overall illness (e.g. APACHE or SAPS score), or b. of ALI or ARDS
iii. aetiology of ALI or ARDS (e.g. septicaemia, pneumonia, trauma, burns, etc)

Mortality and other outcomes have been shown to vary by the age of the patient, the initial severity of the ALI or ARDS or patients condition (e.g. by APACHE score) and by the underlying cause of the ALI or ARDS (Monchi 1998; Ware 2000; Suntharalingam 2001).

Intervention:
i. initial amount or dose of PFC
ii. whether continuous PLV or intermittent doses of PFC
iii. type of PFC (e.g. perflubron, Rimar, etc)

The correct dose of PFC to use when initiating PLV is unknown. Variations in the technique of PLV may also include giving an initial dose of PFC with or without further top-up doses to maintain partial filling of the lungs. Various types of PFC with different physical and chemical properties may be used. (Davies 1999).

Co-interventions:
i. use of inhaled nitric oxide
ii. use of surfactant
iii. use of the prone position
iv. high frequency ventilation

Whilst the mainstay of treatment of ALI or ARDS is mechanical ventilation, additional therapies have been considered and some of these subjected to randomized controlled trials. Adjuncts to mechanical ventilation have included inhaled nitric oxide, endogenous surfactant, prone positioning, and high frequency ventilation (Conner 2000): all can be used in conjunction with PLV.

DESCRIPTION OF STUDIES

Eleven reports of nine studies were initially located by the search strategy. Eight of the studies were excluded (see Table: Characteristics of Excluded Studies). There were no disagreements between reviewers.

Only one study (Fuhrman 1998) was identified and found eligible for inclusion in this review. It has only been reported as an abstract in conference proceedings. We have contacted the first author of this study and the company that sponsored it and no further information or data are forthcoming from either source.

The study ran from January 1996 to April 1997 and enrolled 182 patients in 65 centres. At enrolment patients were allocated to receive either PLV (N=91) or conventional mechanical ventilation (control group, N=91). The study was complicated by the fact that entry criteria, use of other rescue therapies and the primary outcome were modified at least twice during the study. These modifications included liberalization of the entry criteria and allowed use of adjunct therapies in the control group, such as high frequency ventilation and/or inhaled nitric oxide. The study was stopped well short of expected recruitment (less than 20%) because of an "abrupt decline" in mortality in the control group. Mortality at 28 days was 22% in the PLV group and 14% in the control group, but this difference did not reach statistical significance. It is not clear why the study did not continue thereafter. Other outcomes reported for PLV versus control were: overall mortality (not defined) 26% versus 20%; 28 day respiratory mortality 10% versus 10%; ventilator free days (not defined) 10.1 versus 12.4; and air leak 33% versus 30%. None of these outcomes showed statistically significant differences.

METHODOLOGICAL QUALITY

In Fuhrman et al's study (Fuhrman 1998):
- treatment allocation was randomized (exact method not stated);
- whether allocation was adequately concealed is unknown;
- treatment was not blinded;
- follow-up rate not reported;
- whether the published outcomes were assessed by blinded evaluators is unknown (blinding of the assessment of death is not applicable).

The fact that entry criteria, use of other rescue therapies and the primary outcome were modified at least twice during the study, and that these are not adequately described in the abstract, makes it difficult to assess the impact of the modifications on the quality of the data available.

Also, each study centre enrolled an average of only 2.8 patients into the study (182 patients in 65 centres) - many of these centres would only have enrolled one or two patients into the study and many would have only treated one child with PLV. This may have led to wide variation in the application of PLV, the success of which may well be determined in part by how the PLV is applied.

RESULTS

Limited results are available from only one study (Fuhrman 1998) which was stopped prematurely. The only outcome of clinical significance available from the only published report of this trial was 28 day mortality; although not reported we assumed 100% follow-up for analysis of this short-term outcome. There was no statistically significant difference between groups for this outcome with a relative risk for 28 day mortality in the PLV group of 1.54 (95% confidence intervals of 0.82 to 2.9).

DISCUSSION

The study by Fuhrman et al (Fuhrman 1998) was stopped prematurely and was therefore under-powered to detect any significant differences. The wide 95% confidence intervals for 28 day mortality mean that a clinically significant difference cannot be excluded.

While it has been suggested that PLV is a promising alternative mode of mechanical ventilation for children with ALI or ARDS, there are no data from adequately powered RCTs available to determine whether PLV is effective or not in decreasing morbidity or mortality.

It is unfortunate that the only RCT investigating PLV in children with ALI or ARDS done so far (Fuhrman 1998) has not been published in full or that data on more clinically relevant outcomes (especially mortality at discharge and later, duration of respiratory support and hospital stay, and long term neurodevelopmental outcomes) is not forthcoming from the study investigators or the company that sponsored the trial. The limited information available from the published abstract of this study makes it difficult to make a complete assessment of study quality.

The under-reporting of RCTs due to publication bias has been well described (Dickersin 1987; Dickersin 1990; Dickersin 1993). In a systematic review of pharmaceutical industry sponsorship and research outcome Lexchin et al (Lexchin 2003) found that research funded by drug companies was less likely to be published. Some consider the selection of reports for publication on the basis of "positive results", or the failure of investigators to publish results with sufficient detail to allow judgments to be made about their validity as scientific misconduct (Chalmers 1990). It is unknown whether any of these factors are operating here.

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence from RCTs to support or refute the use of PLV in children with ALI or ARDS.

Implications for research

If children with ALI or ARDS are to be treated with PLV then adequately powered, high quality RCTs are still needed to assess its efficacy. Clinically relevant outcome measures should be assessed (especially mortality at discharge and later, duration of respiratory support and hospital stay, and long term neurodevelopmental outcomes) and the studies should be published in full.

POTENTIAL CONFLICT OF INTEREST

None known.

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Zilberberg 1998
Zilberberg MD, Epstein SK. Acute lung injury in the medical ICU: comorbid conditions, age, etiology, and hospital outcome. *American Journal of Respiratory and Critical Care Medicine* 1998;**157**(4 Pt 1):1159–64.

* *Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	**Fuhrman 1998**
Methods	RCT method of randomization - unknown allocation concealment -

Characteristics of included studies (*Continued*)

	unknown
Participants	182 "paediatric patients" with ARDS all had PaO2/FiO2 ratio <200mmHg with bilateral infiltrates there were three enrolment periods which differed in the "entry criteria, use of rescue therapies and primary outcome endpoint."
Interventions	control group - conventional mechanical ventilation (and/or HFOV) treatment group - partial liquid ventilation during 3rd enrolment period HFOV and/or iNO were allowed, though not during PLV it is unknown whether children in the control group would have had HFOV/NO whilst in the study when children in the PLV group would not have had these treatments
Outcomes	28 day mortality overall mortality 28 day respiratory mortality ventilator free days air leak
Notes	
Allocation concealment	B

Characteristics of excluded studies

Fedora 1999	no control group, not randomized
Gauger 1996	no control group, not randomized
Gentili 2000	no control group, not randomized
Greenspan 1997	no control group, not randomized
Hirschl 1995	no control group, not randomized
Meaney 1997	no control group, not randomized
Nekvasil 1996	no control group, not randomized
Toro-Figueroa 1996	no control group, not randomized

ANALYSES

Comparison 01. Partial liquid ventilation versus conventional mechanical ventilation

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 28 day mortality			Relative Risk (Random) 95% CI	Totals not selected

INDEX TERMS

Medical Subject Headings (MeSH)

Adolescent; Child; Child, Preschool; Infant; Infant, Newborn; *Liquid Ventilation; Respiratory Distress Syndrome, Adult [complications; mortality; *therapy]; Respiratory Distress Syndrome, Newborn [complications; mortality; *therapy]

MeSH check words

Humans

COVER SHEET

Title	Partial liquid ventilation for the prevention of mortality and morbidity in paediatric acute lung injury and acute respiratory distress syndrome
Authors	Davies MW, Sargent PH
Contribution of author(s)	MWD - conceived the question, wrote the protocol, searched for studies, assessed all potential studies for inclusion, extracted data, analysed the results and wrote the review. PHS - co-wrote protocol, searched for studies, assessed all potential studies for inclusion, extracted data, analysed the results and co-wrote the review.
Issue protocol first published	2002/4
Review first published	2004/2
Date of most recent amendment	11 February 2005
Date of most recent SUBSTANTIVE amendment	23 July 2004
What's New	Information not supplied by author
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	Information not supplied by author
Date authors' conclusions section amended	Information not supplied by author
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Editorial group	Cochrane Anaesthesia Group
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GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Partial liquid ventilation versus conventional mechanical ventilation, Outcome 01 28 day mortality

Review: Partial liquid ventilation for the prevention of mortality and morbidity in paediatric acute lung injury and acute respiratory distress syndrome

Comparison: 01 Partial liquid ventilation versus conventional mechanical ventilation

Outcome: 01 28 day mortality

Study	PLV n/N	CMV n/N	Relative Risk (Random) 95% CI	Relative Risk (Random) 95% CI
Fuhrman 1998	20/91	13/91		1.54 [0.82, 2.90]