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A multi-centre, double-blind, placebo-controlled study of liposomal prostaglandin E1 (TLC C-53) in patients with acute respiratory distress syndrome

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Abstract *Objective*: To evaluate the safety of liposomal PGE1 (TLC C-53) in patients with acute respiratory distress syndrome (ARDS), and determine its efficacy in improving oxygenation and reducing ventilator dependency.
Design: A multi-centre, randomized, double-blind, placebo-controlled clinical study.
Setting: Thirty-one hospitals in six European countries.
Patients: One hundred two patients with ARDS.
Interventions: Patients were randomized in a 2:1 ratio to receive infusions of either the study drug TLC C-53 or placebo. Infusions were given over 60 min every 6 h for 7 days. The dose of study drug started at 0.6 μg/kg per h, rising over 24 h to a maximum dose of 1.8 μg/kg per h.
Measurements and main results: Seventy patients received the study drug and 32 placebo. Sixty-nine patients (47 treatment, 22 placebo) completed the study protocol. Patients were monitored for changes in the PaO_2/FIO_2 ratio, changes in lung compliance, time to off-ventilator and 28-day mortality, in addition to basic haematological and haemodynamic parameters. There were no significant differences in demographics and baseline characteristics between the two groups. There were no differences in the time to off-ventilation (16 days with treatment, 16.6 days with placebo, $p = 0.94$) or in 28-day mortality (30 % with treatment, 28 % with placebo, $p = 0.78$). There was a difference in the time to achieve a PaO_2/FIO_2 ratio above 300 in favour of TLC C-53 (10.3 versus 26.5 days) but this was not statistically significant ($p = 0.23$).
Conclusions: TLC C-53 was generally well-tolerated but failed to reduce mortality or duration of mechanical ventilation.

Keywords Mechanical ventilation · Oxygenation · Acute respiratory failure · Neutrophils · Immunotherapy · Outcome

Introduction

Mortality rates in acute respiratory distress syndrome (ARDS) remain high despite advances in our understanding of the pathogenetics of ARDS and in our treatment strategies. Many clinical conditions have been associated with the development of ARDS, but whatever the underlying cause, an inflammatory response is apparent. This is associated with the release of inflammatory mediators such as tumour necrosis factor (TNF) and interleukin-1 (IL-1), complement activation, neutrophil activation and aggregation, production of cyclooxygenase and lipoxygenase products, platelet aggregation, release of reactive oxidant species, etc. The end result is disrupted capillary endothelial integrity with interstitial oedema formation, tissue injury, respiratory failure, decreased systemic oxygenation and ultimately death.

Prostaglandin E1 (PGE1) is a pulmonary and systemic vasodilator which can modulate neutrophil function [1] and inhibit mediator release [2]. It may, therefore, be expected to have a beneficial role to play in the treatment of ARDS. Indeed, in animal studies, PGE1 has been shown to reduce neutrophil aggregation and pulmonary capillary leak in various models of lung injury [3, 4]. However, initial clinical studies with PGE1 showed no benefit on survival [5]. One suggestion for this apparent failure of treatment was that free PGE1 was not able to target neutrophils sufficiently at doses which would not cause systemic toxicity [6] and the use of liposome-entrapped PGE1 was proposed. Liposomes are microscopic vesicles composed of one or more lipid membranes surrounding discrete aqueous compartments. Water-soluble compounds can be encapsulated in these aqueous spaces and lipid-soluble drugs can be incorporated in the lipid membranes. Liposomes release their contents by interacting with various cell types, including the neutrophil, and accumulate preferentially at sites of inflammation [7]. Entrapment of PGE1 in liposomes could thus provide a means of more selectively delivering the PGE1 to its target in acute lung injury, the neutrophil.

Importantly, liposomal PGE1 influences neutrophil function through both its PGE1 and liposome fractions, with additive effects. Empty liposomes are opsonized by various compounds including the complement fragment C3bi. Neutrophil receptors for these compounds are upregulated when neutrophils are activated, potentially enhancing the interaction of PGE1 with its receptor. In addition, when liposomes or PGE1 bind to neutrophil receptors the result is an increase in cAMP levels and the combined administration of liposome-entrapped PGE1 has an additive effect on cAMP levels, providing an effect on neutrophil function stronger than the two compounds given individually. Indeed, in a study of IL-1-induced neutrophil accumulation and lung leak in rats, Leff et al. [6] showed that PGE1 entrapped in liposomes decreased lung leak and neutrophil accumulation, while neither liposomes nor PGE1 alone had any effect. Other animal studies of neutrophil-mediated inflammatory disease processes have shown reduced neutrophil accumulation and improved survival with liposomal PGE1 [8, 9, 10].

In a small phase II clinical trial in ARDS patients, liposomal PGE1 treatment improved oxygenation and reduced ventilator dependency [11]. The current multicentre trial was designed to confirm these initial encouraging results.

Methods

The study was approved by the institutional ethics committees and written informed consent was received from each patient or his/her closest relative. Consecutive patients with ARDS were randomized 2:1 to receive infusions of either the study drug TLC C-53 or placebo. Inclusion criteria were: a diagnosis of ARDS (as defined by the American-European consensus conference [12], i.e., presence on chest X-ray of new, bilateral pulmonary infiltrates and a PaO_2/FIO_2 ratio < 200 mmHg measured less than 24 h before study enrolment; a pulmonary capillary wedge pressure [PCWP] ≤18 mmHg; need for mechanical ventilation; age at least 18 years and an expected survival of at least 7 days). Exclusion criteria were: pregnancy; PCWP higher than 18 mmHg; presence of, or suspected, neurogenic pulmonary oedema; hypersensitivity to prostaglandin, eggs or egg products; serum creatinine 4.0 mg/dl or more; serum bilirubin 4.0 mg/dl or more; severe chronic cardiac failure (NYHA ≥ class III); neutrophil count lower than 1000/mm^3; acute myocardial infarction within 6 weeks, pneumonectomy; participation in an investigational drug study within 30 days of enrolment; treatment with a non-proven therapy for the present ARDS episode; continuous intravenous administration of nitroprusside, nitroglycerin or labetolol; treatment with misoprostol or alprostadil. Patients received standard medical/surgical care during the study period, with no special guidelines regarding ventilatory, vasopressor or fluid strategies. The use of inhaled nitric oxide was allowed only after completion of the second infusion of the study drug and then only if the patient had a PaO_2/FIO_2 ratio below 125 mmHg for more than 2 h despite optimization of mechanical ventilation.

Prostaglandin E1 or placebo were infused over a 1-h period every 6 h for 7 days. The initial four infusions used a rising dose regimen (0.6 μg/kg per h for doses 1 and 2, 1.2 μg/kg per h for doses 3 and 4), after which a fixed dose of 1.8 μg/kg per h was administered every 6 h to the end of the 7-day study period, as tolerated. Placebo-treated patients received an equivalent volume of D5 W for injection. Intolerance was defined as the development of clinically significant drug-related side effects including hypotension and hypoxaemia. If a patient was intolerant to an increase in dose, the rate of infusion was reduced by a half and, if necessary, a quarter of the previous rate. If intolerance continued, the infusion was stopped. The next dose was then commenced at the previously tolerated level. If two consecutive doses required rate reductions and intolerance persisted, no further study drug administration was offered.

During the study period patients were monitored for vital signs (blood pressure, pulse, temperature, respiratory rate) immediately before and 10, 30 and 45 min after each study drug infusion, com-

plete physical examination (baseline and at 7 days), routine haematological and chemistry tests (baseline and days 3, 5 and 7), arterial blood gases (daily if intubated), type and mode of mechanical ventilation (daily), SAPS II score, lung injury score, changes in the PaO_2/FIO_2 ratio, changes in lung compliance, chest X-ray (baseline and day 7), electrocardiogram (baseline and days 3, 5 and 7), organ dysfunction (baseline and days 3, 5, and 7), time to extubation, time to off-ventilator, non-ICU days of survival and ventilator-free days of survival. (Organ failure was defined as MAP < 70 mmHg, fluid unresponsive for the cardiovascular system; Glasgow coma score [GCS] < 12 for the neurological system; platelets < $100 \times 10^3/mm^3$ for the coagulation system; creatinine ≥2 mg/dl for the renal system; bilirubin ≥2 mg/dl for the hepatic system and PaO_2/FIO_2 ≤300 mmHg for the respiratory system). Patients who completed the 7-day trial period were also assessed on days 14 and 28.

For statistical analysis, data from all the centres were combined. The time to off-ventilator, time to death and other "time to" events for the TLC C-53 and placebo groups were compared using the Kaplan-Meier product-limit estimate of the respective survival functions. A log rank test of treatment differences was used. The 28-day all cause mortality was compared using the chi-square test. Changes from baseline in the PaO_2/FIO_2 ratio and lung compliance were compared using a one-way analysis of variance. Differences in lung injury score were compared with a Wilcoxon rank sum test. A p value less than 0.05 was considered statistically significant.

Results

The study was powered for 180 patients. However, the trial was discontinued at the planned interim analysis of 100 patients for a failure to meet the end points. A total of 102 patients (69 male, 33 female) were thus randomized; 70 received the study drug and 32 received placebo. Sixty-nine of the 102 patients completed the 7-day study period (47 treatment, 22 placebo). The reasons for not completing the study period were: supportive therapy withdrawn in six patients (4 TLC C-53, 2 placebo); patient improved and was discharged from hospital before day 7 in nine (7 TLC C-53, 2 placebo); adverse event in ten (8 TLC C-53, 2 placebo); significant protocol deviation in one (placebo) and other reasons in seven patients (4 TLC C-53, 3 placebo). Thirty-two patients did not complete the 28-day period, the main reason for this being death (19 in the TLC C-53 group and 9 in the placebo group).

There were no significant differences in demographics or baseline characteristics between the treatment and placebo groups (Table 1). The most common type of pulmonary injury was diffuse pulmonary infection (26% for TLC C-53, 34% for placebo) and/or sepsis (47% for TLC C-53, 34% for placebo) (Table 2). There were no significant differences in the type of ventilatory support provided, the majority of patients in both groups being ventilated using pressure-control ventilation. There was no significant difference in the time to off-ventilation (16 days treatment versus 16.6 days placebo, $p = 0.94$) or in 28-day mortality (30% treatment versus 28% placebo, $p = 0.78$). There was an apparent reduction in the time to achieve a PaO_2/FIO_2 ratio above 300 mmHg, but this was not statistically significant (10.3 days treatment versus 26.5 days placebo, $p = 0.23$) (Fig. 1).

Table 1 Baseline characteristics in treatment and placebo patients (mean ± SD)

	TLC C-53	Placebo	p value
Age (years)	50 ± 19	56 ± 18	0.13
Sex (male:female)	47:23	22:10	0.87
Lung injury score	2.9 ± 0.6	2.9 ± 0.6	0.58
SAPS II	45.7 ± 16.3	45.4 ± 13.5	0.94
PaO_2/FIO_2 (mmHg)	145 ± 73	143 ± 70	0.90
Bilirubin (μmol/l)	18.7 ± 18.1	21.1 ± 16.8	0.54
Neutrophil count ($x10^9$/l)	9.3 ± 7.2	6.4 ± 5.1	0.41
Onset of ARDS to first dose (h)	6.5 ± 5.9	8.0 ± 6.4	0.26

Table 2 Aetiology of ARDS in the two groups (there were no significant differences between the groups in terms of aetiology). Patients could have more than one aetiological process

	TLC C-53 (%)	Placebo (%)
Direct injury	47 (67)	19 (59)
Aspiration	16 (23)	4 (13)
Diffuse pulmonary infection	18 (26)	11 (34)
Near drowning	2 (3)	0
Lung contusion	10 (14)	4 (13)
Other	4 (6)	3 (9)
Indirect injury	50 (71)	21 (66)
Sepsis	33 (47)	11 (34)
Severe non-thoracic trauma	8 (11)	3 (9)
Hypertransfusion for emergency resuscitation	4 (6)	3 (9)
Cardiopulmonary bypass	1 (1)	1 (3)
Other	11 (16)	6 (19)

Discussion

Prostaglandin E1 is a pulmonary vasodilator which can reduce right ventricular afterload. In oleic acid-induced lung injury in pigs, PGE1 decreased pulmonary artery pressures and reduced the effective pulmonary artery elastance [13]. However, these effects can also result in increased pulmonary shunting of blood with a fall in PaO_2 [13, 14] and systemic vasodilation can reduce mean arterial pressure [13].

Beneficial systemic effects of PGE1 administration have been reported. PGE1 can increase oxygen extraction capabilities when oxygen delivery is acutely reduced [15, 16] and has significant anti-inflammatory effects. Gillespie et al. [17] showed that PGE1 reduced hydrogen peroxide-induced lung damage by inhibiting

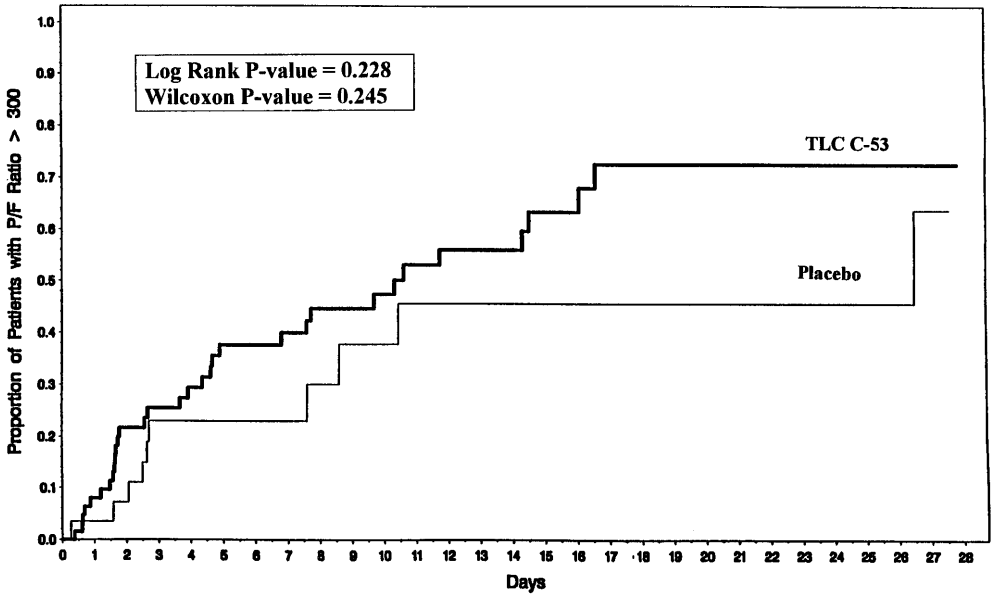

Fig. 1 Time to first PaO_2/FIO_2 ratio above 300, showing non-significant trend in favour of treatment over placebo

the release or actions of lipoxygenase products and PGE1 has been shown to have beneficial effects in models of ischaemia/reperfusion [18, 19] and acute pancreatitis [4].

Several clinical studies on PGE1 in ARDS have now been conducted. In an early study of 41 patients with ARDS, PGE1 infusion improved pulmonary function and 30-day survival [20]. In a study of 18 surgical patients with circulatory deficiencies, Appel and colleagues [21] found that PGE1 improved tissue perfusion. Slotman et al. [22], using 30 ng/kg per min PGE1, noted an increase in cardiac index and oxygen delivery, a decrease in serum bilirubin and SGOT and an increase in white blood cell count, suggesting improved cardiovascular performance, hepatic function and leukocyte availability in ARDS patients. However, Rossignon et al. [23] reported no effects of PGE1 on functional leukocyte activity and, in a randomized controlled trial of 100 patients with ARDS, although there was evidence of improved oxygen availability and consumption in the treated patients, PGE1 treatment had no effect on survival [5, 24]. Russell et al. [25] also failed to demonstrate a beneficial effect of PGE1 (30 ng/kg per min) on organ function or mortality in ARDS patients.

Liposomal PGE1 has enhanced anti-inflammatory effects in experimental models [6, 8, 9, 10] and has been studied in two clinical trials [11, 26]. In a pilot study involving 25 patients with ARDS, Abraham et al. showed that treatment with PGE1 in liposomes (0.15–3.6 μg/kg per h) reduced ventilator dependency and improved lung compliance and function [11]. A large North American trial [26] of 350 ARDS patients recently found that liposomal PGE1 treatment (0.15–3.6 μg/kg per h) was associated with a shorter time to reach a PaO_2/FIO_2 ratio above 300 mmHg, but had no effect on the duration of mechanical ventilation or survival. Interestingly, in a subgroup study from this trial [26], liposomal PGE1 treatment had no effect on exhaled hydrogen peroxide levels [27]. We failed to show any effect of treatment on either lung function or outcome.

Recent years have seen several similarly negative Phase III trials for various immunomodulating anti-sepsis therapies [28, 29, 30, 31] and various explanations for the apparent failure of these drugs have been proposed [32, 33]. An animal model can never reflect the true clinical picture and the use of these drugs in the heterogeneous ICU population will, perhaps inevitably, give different results to those seen in the carefully regimented and controlled animal model, even if species differences are ignored. Problems with definition abound and even if entry for a clinical trial of a proposed new ARDS treatment is restricted to patients with a diagnosis of ARDS according to a consensus-agreed definition, as in our study, this makes no allowance for other factors, such as pre-existing disease and aetiology, which play an important role in determining outcome in the ICU patient. PGE1 acts by inhibiting neutrophil function, in particular the neutrophil release of reactive oxygen species and protease [34], and it may be that it will only be effective in patients with neutrophil abnormalities susceptible to this form of treatment. New techniques are needed to enable us to target new therapies more effectively at populations who are most likely to benefit according to immunological and pathogenetic mechanisms. Indeed, Kunimoto et al. [35] have shown that the effects of PGE1 may differ according to the precise aetiology and severity of lung failure; lung extraction of

PGE1 may be decreased in patients with ARDS and the systemic, potentially harmful, vasodilatory effects of PGE1 may therefore be greater. Aerosolized PGE1 may be an alternative means of delivering this drug directly to the lungs of patients with ARDS [36, 37], avoiding some of the systemic effects.

We acknowledge that our study has some limitations. Firstly, no specific guidelines were provided regarding ventilatory or cardiovascular support during the study period and it is conceivable that, due to the relatively small number of patients included in the study, differences in patient management may have influenced our results. Secondly, PGE1 is known to act by inhibiting neutrophil function and activation and, although overall baseline neutrophil counts were similar in the treatment and placebo groups, no follow-up measures or assessment of anti-oxidant levels are available. It may thus be that treatment was not targeted at those patients most likely to respond. However, our results are similar to those reported recently from North America [26] and, taken together, it seems that intravenous PGE1, with or without liposomes, is unlikely to have a beneficial role in the routine treatment of sepsis or ARDS. Whether it may be effective in selected subgroups of patients remains unanswered.

Appendix: List of participating centres

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