ORIGINAL ARTICLE

Improvements in Lung Preservation: 3 Years' Experience With a Low-Potassium Dextran Solution

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OBJECTIVE: Lung preservation quality is a crucial factor in the success of a lung transplant. In October 2000 we stopped using Euro-Collins (EC) lung preservation solution and began using a low potassium dextran solution (Perfadex [PER]). The objective of the present study was to assess outcome with the 2 solutions.

MATERIAL AND METHODS: We analyzed the results of 68 lung transplants in which PER was used and compared the results with those of a historical control group consisting of the same number of transplants in which EC was used.

RESULTS: There were no significant differences in the ages and diagnoses of the recipients in the 2 groups. Waiting list time was longer in the PER group. The most frequent cause of donor death in the EC group was craniocerebral trauma (62%), whereas in the PER group it was cerebral hemorrhage (54%). In the PER group more double lung transplants were performed than in the EC group (78% and 53% respectively; *P*=.002). There were no differences in the use of extracorporal circulation or ischemia time between the 2 groups. Early graft function, based on the patient's oxygenation index (ratio of PaO_2 to inspired oxygen fraction [FiO_2]) on arrival at the intensive care unit, was similar in the 2 groups. The incidence of severe graft failure (PaO_2/FiO_2<150 mm Hg) was significantly lower in the PER group than in the EC group (16% and 37% respectively; *P*=.01). No significant differences in hours of mechanical ventilation or postoperative mortality between the 2 patient series were found.

CONCLUSIONS: Use of the newer lung preservation solution —PER— led to a 50% lower incidence of severe ischemia-reperfusion graft injury during the early recovery from lung transplantation.

Key words: *Lung transplantation. Ischemia-reperfusion injury. Mortality.*

Mejoras en la preservación pulmonar. Tres años de experiencia con una solución de dextrano bajo en potasio

OBJETIVO: La calidad de la preservación pulmonar es uno de los aspectos más determinantes en el éxito del trasplante pulmonar. En octubre del año 2000 modificamos nuestra solución de preservación pulmonar, que hasta entonces era el Euro-Collins (EC), y comenzamos a utilizar una solución de dextrano bajo en potasio, comercializada como Perfadex (PER). El objetivo de este estudio es analizar los resultados de ambos métodos.

MATERIAL Y MÉTODOS: Hemos analizado los resultados de 68 trasplantes pulmonares con PER y los hemos comparado con los de una serie retrospectiva del mismo número de trasplantes realizados con EC.

RESULTADOS: No existen diferencias significativas respecto a la edad o el diagnóstico de los receptores entre ambos grupos. El tiempo en lista de espera fue mayor en el grupo de PER. La causa de muerte del donante más frecuente del grupo EC fue el traumatismo craneoencefálico (62%), mientras que en el grupo de PER fue la hemorragia cerebral (54%). En el grupo de PER se realizaron más trasplantes bipulmonares que en el de EC (el 78 y el 53%, respectivamente; p = 0,002). No hay diferencias en la indicación de circulación extracorpórea o tiempos de isquemia entre ambos grupos. Se evaluó la función pulmonar temprana a través del índice de oxigenación (PaO_2/FiO_2) a la llegada a la unidad de cuidados intensivos, que fue comparable entre ambos grupos. La incidencia de disfunción grave del injerto (PaO_2/FiO_2 < 150 mmHg) fue significativamente inferior en el grupo de PER frente al de EC (el 16 y el 37%, respectivamente; p = 0,01). No encontramos diferencias significativas respecto a las horas de ventilación mecánica ni en cuanto a la mortalidad postoperatoria entre las 2 series.

CONCLUSIONES: Con la aplicación clínica de esta nueva solución de preservación pulmonar se obtiene una reducción del 50% en la incidencia de la lesión de isquemia-reperfusión grave del injerto en el postoperatorio inmediato del trasplante pulmonar.

Palabras clave: *Trasplante pulmonar. Lesión de isquemia-reperfusión. Mortalidad.*

Introduction

Lung graft ischemia-reperfusion injury continues to be one of the most important complications in the initial phase of a lung transplant. The incidence of such injury

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ranges from 20% to 40% in different transplant programs.[1] Postoperative mortality attributable to ischemia-reperfusion injury has not changed in recent years.[2] Severity and clinical presentation of such injury vary from mild pulmonary signs detected only radiographically to severe complications involving pronounced hypoxemia, incomplete lung expansion, pulmonary hypertension with pulmonary edema, and graft failure.

In this setting numerous studies have been carried out to gain deeper understanding of the pathophysiology of lung graft injury. Specific causal factors have been identified, such as ischemic cell damage, which affects both the epithelial and the endothelial cells of the alveolar-capillary network. Such cell damage leads to the release of inflammatory mediators, which in turn lead to increased capillary permeability and a prolongation and aggravation of tissue injury.[3] Preservation of the alveolar-capillary membrane by an organ-preserving solution that minimizes cell injury during the inevitable period of ischemia is of crucial importance.

The Euro-Collins (EC) solution, which is rich in intracellular potassium ions, has been the most widely used for preservation. However, experimental studies have shown that, compared with the EC solution, an extracellular low-potassium dextran solution results in improved preservation of endothelial function and less toxicity of type-2 pneumocytes.[4,5] Other authors have achieved improved surfactant function and lower incidence of ischemia-reperfusion injury in experimental lung transplants with the low-potassium dextran solution compared to the EC solution.[6] With these precedents, the first reports of clinical experiences with low-potassium solutions showed improved lung graft function in early recovery.[7-9]

Based on these reports, in October 2000 we changed from the EC solution to a low-potassium dextran solution—Perfadex® (Vitrolife, Göteborg, Sweden) (PER)—in our lung transplant program. The objective of the present study was to compare the effects of PER on early lung graft function in a prospective 3-year series of transplant patients with those of a historical patient series in which the EC solution had been used.

Materials and Method

From October 2000 to September 2003, 68 lung transplants were performed in our hospital using PER as the lung preservation solution (Table 1). Information for this patient series was gathered prospectively from data sheets on donors, recipients, and surgical and postoperative procedures. The variables were processed using the computer software program SPSS, version 10.0. The control group comprised a previous series of 68 patients who received EC lung preservation and for whom retrospective data could be gathered. Cardiopulmonary transplants were not included in either of the series. The mean (SD) age of the recipients in the EC group was 43 (12) years (range, 13-65 years) and that of the recipients in the PER group was 43 (15) years (range, 15-65 years). Forty-three patients were men and 25 were women in the EC group; the count was 38 and 30, respectively, in the PER group. Mean transplant waiting list time was 63 (55) days (range, 1-363 days) in the EC group and 120 (118) days (range, 1-517 days) in the PER group ($P<.05$). The diagnoses of the recipients in both series are shown in Table 2. In the PER group 5 patients being mechanically ventilated received transplants and 4 patients received retransplants, whereas the EC group included no patients with such characteristics.

The mean age of the donors was 27 (12) years (range, 7-57 years) in the EC group and 37 (13) years (range, 12-57 years) in the PER group ($P<.01$). The most frequent cause of donor death was craniocerebral trauma (62%) in the EC group and cerebral hemorrhage (54%) in the PER group ($P<.01$). Table 3 shows the distribution of the causes of donor death. Most patients (71%) were men in the EC group, but only 48% were men in the PER group ($P<.01$). Mean mechanical ventilation time for donors until explantation was 42 (33) hours (range, 12-168 hours) in the EC group and 53 (108) hours (range, 12-864 hours) in the PER group. The mean donor oxygenation index (ratio of PaO_2 to inspired oxygen fraction [FiO_2]) before aortic clamping was 439 (89) mm Hg (range, 234-640 mm Hg) in the EC group and 447 (86) mm Hg (range, 284-637 mm Hg) in the PER group. Donors were screened according to radiographic and bronchoscopic findings, pulmonary macroscopic inspection, and gasometry. Preservation procedure systematically included 500 mg of intravenous methylprednisolone and a 1-mg bolus dose of prostaglandin E_1 infused into the pulmonary artery just before aortic clamping. As reported,[10] our transplant group infuses the preservation solution in 2 steps (first retrograde and then

TABLE 1
Composition of Euro-Collins (EC) and Perfadex® (PER) Preservation Solutions

Composition	EC	PER
Na^+, mmol/L	10	138
K^+, mmol/L	115	6
Phosphate, mmol/L	57.5	0.8
Sulphate, mmol/L	0	0.8
Bicarbonate, mmol/L	10	0
Cl^-, mmol/L	15	142
Glucose, g/L	3.5	0.9
Dextran, g/L	0	5

TABLE 2
Recipients According to Diagnosis*

Diagnosis	EC (%)	PER (%)
Obstructive	40	32
Restrictive	34	40
Suppurative	26	22
Retransplant	–	6

*EC indicates Euro-Collins preservation solution; PER, Perfadex® preservation solution.

TABLE 3
Causes of Donor Death*

Diagnosis	EC (%)	PER (%)
Cerebral hemorrhage	35	54
Craniocerebral trauma	62	37
Other	3	9

*EC indicates Euro-Collins preservation solution; PER, Perfadex® preservation solution.

anterograde), a technique we applied in both the EC and PER groups in the present study, administering approximately 60 mL/kg of preservation solution.

To assess early lung graft function we measured arterial gases with the oxygenation index PaO_2/FiO_2 within the first 2 hours of the patient's arrival at the intensive care unit. Development of severe ischemia-reperfusion injury was considered when the oxygenation index was less than or equal to 150 mm Hg. Mechanical ventilation time was defined as the number of hours the patient was ventilated from admission to extubation or disconnection from the respirator. If the patient was extubated but tubes were reinserted within 72 hours, the extubation was not counted. Postoperative mortality was defined as that occurring while the patient was still in the intensive care unit.

Statistical Analysis

For our statistical analysis we used the χ^2 test to compare proportions, and the Student *t* test and the Mann-Whitney U test to compare means. Data are shown as means (SD). $P<.05$ was considered a statistically significant value.

Results

Thirty-six (53%) double lung transplants and 32 (47%) single lung transplants were performed in the EC group compared to 53 (78%) and 15 (22%), respectively, in the PER group ($P=.002$). Extracorporal circulation was required in 13 (19%) transplants in the EC group and in 17 (25%) in the PER group. Mean ischemia time for single lung transplants was 258 (64) minutes (range, 120-420 minutes) in the EC group and 296 (68) minutes (range, 195-420 minutes) in the PER group. For double lung transplants mean ischemia time for the first lung was 229 (56) minutes (range, 135-350 minutes) in the EC group and 264 (68) minutes (range, 155-500 minutes) in the PER group; mean ischemia time for the second lung was 345 (64) minutes (range, 240-510 minutes) in the EC group and 399 (82) minutes (range, 270-665 minutes) in the PER group.

We found no significant differences between either group regarding mean oxygenation index on arrival at the intensive care unit: 238 (124) mm Hg (range, 53-557 mm Hg) in the EC group and 257 (108) mm Hg (range, 60-510 mm Hg)—slightly higher—in the PER group. We noted significantly fewer incidences of ischemia-reperfusion injury in the PER group (16%) compared to the EC group (37%) ($P=.01$). Mechanical ventilation time was similar in both groups: 174 (259) hours (range, 2-1104 hours) in the PER group and 182 (296) hours (range, 6-1272 hours) in the EC group. No significant difference was found in postoperative mortality: 22% in the EC group and 20% in the PER group.

Discussion

We are aware that the use of a historical control group is a design limitation of the present study. Therefore, although we made no substantial changes in our lung transplant protocol regarding selection of donors, explantation technique, implantation technique, and perioperative management of patients during either period, there were some differences between the series that should be taken into consideration. During the last decade the main cause of donor brain death has changed. At present more donors have died of cerebral hemorrhage, whereas in the past, more had head injury. As a consequence, the proportion of female donors has risen, as has the mean age of all donors. Despite such changes, there are no differences between the series we compared in the present study regarding donor oxygenation before aortic camping, indicating that the impact of these changes on the initial outcome of transplantation would seem to be minimal.

Although there were no differences in recipient diagnoses between the two groups compared, the PER group included patients under invasive mechanical ventilation and retransplant patients. The comorbidity and greater technical difficulty that such cases involve may be associated with poorer early graft function, longer time under mechanical ventilation, and higher postoperative mortality rates. The PER group had a larger proportion (nearly 80%) of patients who received double lung transplants. This figure reflects a tendency among transplant groups in Spain, who favor double lung transplants over single lung transplants in order to avoid perioperative problems caused by the native lung.

Even taking into account the aforementioned design limitations, it is still evident that the incidence of ischemia-reperfusion injury in the PER group was superior. The change to the PER solution has reduced the incidence of early graft dysfunction by more than half compared to the historical EC control group. In the present study, unlike others,[7-9] we have not shown that PER preservation improved ventilation time or mortality in comparison to EC. Various factors may have influenced the lack of consistency between our results and others', such as inclusion of less optimal recipients in the PER group (patients under mechanical ventilation and retransplant patients). In a larger patient series PER might lead to significantly different results with regard to ventilation and mortality.

We conclude that, despite the limitations of the present study, clinical application of the new lung preservation solution, PER, has resulted in a significant reduction in the incidence of severe ischemia-reperfusion injury during early recovery from lung transplantation.

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