Value of Preoperative Use of Statins as a Protective Factor for Severe Graft Dysfunction After Lung Transplantation: A Multicenter Propensity Score Analysis

La utilidad del uso de estatinas de forma preoperatoria como factor protector de la disfunción grave del injerto tras un transplante de pulmón: un análisis multicéntrico con emparejamiento por índice de propensión

Dear Editor,

Lung transplantation (LT) is the only effective treatment available for some patients with end-stage lung disease. Despite improvements in surgical and medical care, LT is associated with considerable morbidity and mortality. Primary graft dysfunction (PGD) is a syndrome of acute lung injury occurring in the early stage post-lung transplantation.[1] PGD is the main cause of mortality in the first month of transplant and the second cause during the first year.[2]

Statins, 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors, have been described as the most effective class of drugs to reduce serum cholesterol levels.[3] In recent years, it has also been reported that statins have a variety of immunomodulatory and antiinflamatory effects unrelated to their cholesterol-lowering function[3–6] and could have a positive impact on LT recipients. A few studies have reported that dyslipidaemia is an independent risk factor for PGD[7] and that perioperative use of statins is independently associated with reduced risk for PGD.[8]

We report a retrospective, multicenter cohort study aiming to evaluate the impact of recipient preoperative statin therapy on the development of PGD on adult patients undergoing first time uni- or bilateral lung transplantation from brain death donors at four transplant centres in Spain, (January 2015 to December 2017). Comparison was made between groups according to whether the recipient had previously used statins (rSG) or not (rNSG) as dyslipidemia treatment. All centres followed recipient acceptance criteria established by the Organizacion Nacional de Trasplantes (ONT).[9] PGD incidence and its severity, as well as 30, 90 and 360-day survival rate were analyzed. International Society for Heart and Lung Transplantation (ISHLT) Working Group criteria for the definition and severity grading of PGD were used.[1]

Categorical variables are expressed as percentages. Quantitative data are presented as mean and standard deviation (SD) if normally distributed or median if otherwise. The paired *t* test or the *U*-Mann–Whitney test and the Chi-square test or Fisher's exact test were used to compare continuous and categorical variables, respectively. Propensity score was calculated through a multivariate analysis including those variables that were found significantly different ($p < 0.05$) between SG and NSG in the univariate analysis. An univariate analysis was performed in those patients developing PGD, trying to identify the factors impacting on its severity (PGD 3 vs. PGD 1–2). Logistic regression model for PGD severity was built including those variables with $p \leq 0.1$ in the univariate analysis.

A total of 474 consecutive first single and double adult LT procured from 387 brain death donors were included. One hundred and ten recipients (SG, 23.2%) were under statins treatment before transplantation (Table 1).

Global PGD incidence was 34%, with no significant difference between groups. However a significantly lower incidence of grade 3 PGD (37.2% vs. 56.9%, $p = 0.036$) (Fig. 1), as well as better 30d survival (100% vs. 96%, $p = 0.028$) was observed in rSG. No differences in mortality at 60 (94 vs 94, $p = 0.91$) and 90 (85 vs 86, $p = 0.75$) days were found between groups.

The influence of statin treatment on lung donors before retrieval was analyzed with no differences observed between the group taking statins and the one not taking in incidence (38.7% vs. 36.2%, $p = 0.69$) and severity of PGD (PGD1 6.9 vs. 22.1, PGD2 34.5 vs. 29.2, PGD3 58.6 vs. 48.7; $p = 0.176$)

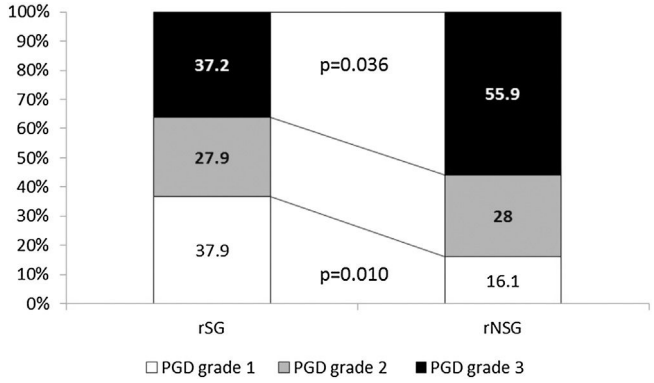

Fig. 1. Primary graft dysfunction severity percentage according to statin treatment groups. PGD: primary graft dysfunction; rSG: recipients statin group; rNSG: recipients no statin group.

Patients developing grade 3 PGD had higher body mass index (BMI) than those developing milder PGD grades. Similarly, more recipients developing grade 3 PGD had not received pre-transplant statin therapy, required hemoderivate transfusion and underwent cardiopulmonary bypass during surgery than those patients developing PGD grade 1 or 2. We analyzed the impact of recipient's disease in PGD's incidence between PGD grade 1–2 and 3 and no statistical differences were seen (COPD 49.1% vs.50.9%, restrictive 50% vs. 50%, Cystic Fibrosis/Bronchiectasis 53.8% vs. 46.2%, primary pulmonary hypertension 60% vs. 40% other 0% vs. 100%; $p = 0.347$)

Multivariate analysis identified the need for hemoderivate transfusion in the recipient during surgery as a factor associated with higher severity of PGD (OR 4.65, 1.27–17.04 $p = 0.02$). Similarly the use of statins showed a trend towards statistical significance(OR 2.28, 0.69–7.57 $p = 0.17$).

This is, to our knowledge, the first multicentric study analyzing the effect of preoperative use of statins in LT recipients and their immediate outcomes. Several authors have evaluated the impact of statins on LT outcome, however these studies were performed in a single centre or evaluated the impact of recipient pretransplant dyslipidaemia[7] or perioperative treatment with statins[8] on transplant outcomes.

We observed a PGD incidence of 34%, similar to data reported in the literature that ranges from 30% to 50% early after transplant.[10] In the present study, recipient's preoperative statin treatment was associated with a significant decrease in the incidence of severe PGD. Raphael et al.[8] reported a decreased incidence of PGD grade 3 in those recipients using statins perioperatively (34.8% vs. 57.9%, $p = 0.001$). However, the study was performed in a retrospective analysis of 266 patients undegoing LT in a single centre.

The presence of PGD has been shown to be associated with higher postoperative 30-day,[11] and 90-day mortality[12] after transplant. Kreisel et al.,[13] described a 1-year survival of 72.8% on those lung recipients developing PGD. We report higher 30-day, 90-day and 1-year survival in those patients developing PGD grade 3 than the one reported by Kreisel. Moreover, in our study recipients in the SG had a significantly decreased 30-day mortality when compared to those not taking statins.

The antioxidant action of statins has been proposed as a potential mechanism by which these agents may improve endothelial function against oxidative stress,[14] reported as an important factor in the pathogenesis of PGD.[15] Recent data also reveals the anti-inflammatory effect of statins due to their potent inhibitory action against the induction of several proinflammatory cytokines.[3] Mur-

Table 1
Donor and recipients' characteristics according to statin pretransplant treatment in the recipient.

Variable	No statins (*N* = 364)	Statins (*N* = 110)	*p*
Recipient			
Clinical data			
Age, years, mean (SD)	53 (12)	60 (7)	**<0.001**
Gender (%)			**0.025**
Male	222 (61.0)	80 (72.7)	
Female	142 (39.0)	30 (27.3)	
BMI, kg/m^2, mean, (SD)	24.8 (4.2)	26.3 (3.8)	**0.001**
Disease			**0.005**
Restrictive	170 (46.7)	58 (52.7)	
COPD	123 (33.8)	45 (40.9)	
CF/BC	39 (10.7)	1 (0.9)	
PPH	18 (4.9)	1 (0.9)	
Other	14 (3.8)	5 (4.5)	
Surgical data			
Blood transfusion (%)			0.454
Yes	134 (47.9)	39 (43.3)	
No	146 (52.1)	51 (56.7)	
Vasoactive drugs (%)			**<0.001**
Yes	224 (77.8)	53 (58.9)	
No	64 (22.2)	37 (41.1)	
CPB (%)			0.159
Yes	60 (20.7)	25 (27.8)	
No	230 (79.3)	65 (72.2)	
Ischaemic time first graft, min, mean (SD)	269 (72)	275 (69)	0.285
Ischaemic time second graft,min, mean (SD)	393 (322)	362 (98)	0.695
Donor[a]			
Clinical data			
Age, years, mean (SD)	53 (13)	56 (13)	**0.008**
Gender (%)			0.112
Male	177 (48.6)	44 (40.0)	
Female	187 (51.4)	66 (60.0)	
BMI, kg/m^2, mean, (SD)	25.9 (4.1)	26.4 (4.2)	0.205
PaO_2, mmHg, mean (SD)	444 (79)	438 (84)	0.507
Smoking			0.305
No smoking (%)	203 (60.8)	61 (61.0)	
Smoking (%)	91 (27.2)	32 (32.0)	
Former smoking (%)	40 (12.0)	7 (7.0)	
Surgical data			
Blood transfusion (%)			1.000
Yes	3 (5.4)	1 (3.4%)	
No	53 (94.6)	28 (96.6)	
Vasoactive drugs (%)			0.514
Yes	74 (85.1)	41 (89.1)	
No	13 (14.9)	5 (10.9)	

BMI: body mass index; CPB: cardiopulmonary bypass; CF/BC: fibrosis/bronchiectasis; PPH: primary pulmonary hypertension.
[a] Donor analysis according to recipient's treatment.

phy et al.[5] reported the ability of simvastatin to attenuate the ex vivo production of epithelium-derived mediators of neutrophilic airway inflammation. Similarly the identification of several mechanisms through which statins may decrease the recruitment of monocytes and T cells and inhibit T cell activation and proliferation has prompted the view that statins could be beneficial in organ transplant recipients.[14] Finally statins inhibit the transcription of major histocompatibility complex class II molecules[16] and up-regulate T-cells, which is associated with improved early graft function after LT in mice and in humans.[17]

In conclusion, our results show that preoperative statin therapy in LT recipients might decrease the incidence of severe PGD and improve 30d survival. Future adequately powered prospective studies are needed to determine the real role of statins in the lung transplant procedure, as well as the identification of type and optimal dosage of statins that will better help to decrease the risk of PGD development.

Disclosure statement

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

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Outpatient management of persistent air leak*

Tratamiento ambulatorio de la fuga aérea persistente

To the Editor

Air leaks are a common problem in thoracic surgery and occur at a rate of 26%–54% on the first postoperative day. Postoperative persistent air leak (PAL) is defined as leak persisting after the third day after surgery according to Brunelli et al.[1], after the fourth day according to Cerfolio et al.[2], and after the fifth day according to Varela et al.[3].

More than 50% of patients undergoing pleural drainage (PD) for pneumothorax develop air leaks at 48 h[4]. The prevalence of PAL varies between 8% and 20%, and is more common in spontaneous secondary pneumothorax[5]. Portable devices, such as the Heimlich valve (HV)[6], are an accepted strategy in patients with high surgical risk[7]. HV reduces drainage and hospitalization time[5].

The aim of this study was to confirm the safety of HV in patients with postoperative PAL and pneumothorax and to determine its economic benefit.

We performed a descriptive study of a cohort of patients with PD and HV for PAL at hospital discharge between January 2013 and May 2020; the sample size was determined by this time period.

For inclusion, patients had to have PAL after pneumothorax or surgery, they had to be stable, and they had to be independent or have good family support. Exclusion criteria were loss to follow-up, HVs in hospitalized patients, and devices used as a bridge to surgery.

Patients were followed up on an outpatient basis with check-ups every 48–72 h, and PD was withdrawn after radiological revision 24 h after clamping.

The main variables were success rate, proportion of patients with resolved PAL after HV placement, and cost saved per treatment. Epidemiological, clinical, and radiological variables were studied as independent variables.

Mean, standard deviation, and percentiles were calculated for quantitative variables, and frequency and percentages for qualitative variables. The Kolmogorov–Smirnov test was used to determine the normality of the data, the Mann–Whitney U test was used to compare the time distribution between 2 groups, and the Kruskall–Wallis test was used for more than 2 groups. Multiple linear regression with the genetic algorithm technique was used to obtain the most parsimonious model and the bootstrapping technique was used as a non-parametric method. Fisher's exact test was used to determine the relationship between qualitative variables.

Mean age was 57 ± 17 years; 73% were men. Overall, 69% of PAL cases occurred after thoracic surgery, 34% of which were major pulmonary resections, and 48% were minor; 3% occurred after primary spontaneous pneumothorax, 26% after secondary pneumothorax, and 2% were iatrogenic, for a total of 105 cases in 98 patients.

Respiratory history of the series is shown in Fig. 1. Almost one third (30%) of patients had 1 previous event, 30% had 2, 14% had 3, 10% had 4, and 2% had 5.

Overall, 64% of the X-rays prior to HV placement showed an air pocket of less than 20% and 28% showed full expansion of the lung. After withdrawal of the PD and HV, 36% had an air pocket of less than 10%, 44% had lung expansion, and 9.5% had complete pneumothorax. PD was placed for a mean of 16 ± 8 days and HV for a mean of 7.5 ± 5.2 days.

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