Arch Bronconeumol. 57 (2021) 706–725

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; $p = 0.176$)

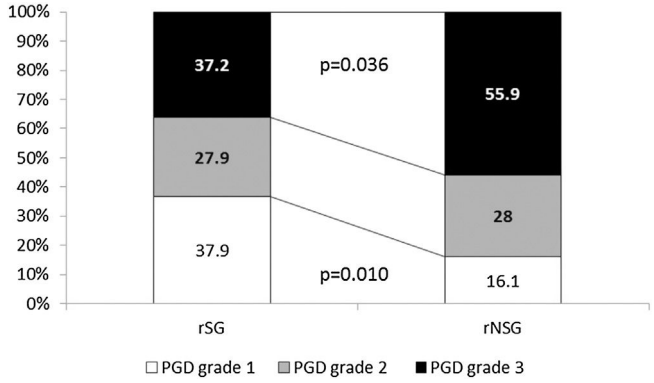

Fig. 1. Primary graft dysfunction severity percentage according to statin treatment groups. PGD: primary graft dysfunction; rSG: recipients statin group; rNSG: recipients no statin group.

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.

Acknowledgements

Writing support was provided by Fidelma Greaves.

Bibliografía

1. Snell GI, Yusen RD, Weill D, Strueber M, Garrity E, Reed A, et al. Report of the ISHLT Working Group on Primary Lung Graft Dysfunction, part I: Definition and grading—A 2016 Consensus Group statement of the International Society for Heart and Lung Transplantation. J Hear Lung Transplant. 2017;36:1097–103.
2. Goldfarb SB, Levvey BJ, Cherikh WS, Chambers DC, Khush K, Kucheryavaya AY, et al. Registry of the International Society for Heart and Lung Transplantation: Twentieth Pediatric Lung and Heart-Lung Transplantation Report—2017; Focus Theme: allograft ischemic time. J Hear Lung Transplant. 2017;36:1070–9.
3. Bedi O, Dhawan V, Sharma PL, Kumar P. Pleiotropic effects of statins: new therapeutic targets in drug design. Naunyn Schmiedebergs Arch Pharmacol. 2016;389:695–712.
4. Youssef S, et al. The HMG-CoA reductase inhibitor, atorvastatin, promotes a Th2 bias and reverses paralysis in central nervous system autoimmune disease. Nature. 2002;420:78–84.
5. Murphy DM, Forrest IA, Corris PA, Johnson GE, Small T, Jones D, et al. Simvastatin attenuates release of neutrophilic and remodeling factors from primary bronchial epithelial cells derived from stable lung transplant recipients. Am J Physiol Cell Mol Physiol. 2008;294:L592–9.
6. Kobashigawa JA. Statins in solid organ transplantation: is there an immunosuppressive effect? Am J Transplant. 2004;4:1013–8.

7. Cottini SR, Ehlers UE, Pagnamenta A, Brandi G, Weder W, Schuepbach RA, et al. Pretransplant dyslipidaemia influences primary graft dysfunction after lung transplantation. Interact Cardiovasc Thorac Surg. 2016;22:402–5.
8. Raphael J, Colling SR, Wang XQ, Scalzo DC, Singla P, Lau CL, et al. Perioperative statin use is associated with decreased incidence of primary graft dysfunction after lung transplantation. J Hear Lung Transplant. 2017;36:948–56.
9. Weill D, Beden C, Corris PA, Dark JH, Davis RD, Keshavjee S, et al. A consensus document for the selection of lung transplant candidates: 2014—an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. J Hear Lung Transplant. 2015;34:1–15.
10. Diamond JM, Arcasoy S, Kennedy CC, Eberlein M, Singer JP, Patterson GM, et al. Report of the International Society for Heart and Lung Transplantation Working Group on Primary Lung Graft Dysfunction, part II: Epidemiology, risk factors, and outcomes—A 2016 Consensus Group statement of the International Society for Heart and Lung Tran. J Hear Lung Transplant. 2017;36:1104–13.
11. Christie JD, Bellamy S, Ware LB, Lederer D, Hadjiliadis D, Lee J, et al. Construct validity of the definition of primary graft dysfunction after lung transplantation. J Hear Lung Transplant. 2010;29:1231–9.
12. Whitson B, Nath D, Johnson A. Risk factors for primary graft dysfunction after lung transplantation. J Thorac. 2006.
13. Kreisel D, Krupnick AS, Puri V, Guthrie TJ, Trulock EP, Meyers BF, et al. Short- and long-term outcomes of 1000 adult lung transplant recipients at a single center. J Thorac Cardiovasc Surg. 2009;141:215–22.
14. Palinski W, Tsimikas S. Immunomodulatory effects of statins: mechanisms and potential impact on arteriosclerosis. J Am Soc Nephrol. 2002;13:1673–81.
15. Cantu E, Lederer DJ, Meyer K, Milewski K, Suzuki Y, Shah RJ, et al. Gene set enrichment analysis identifies key innate immune pathways in primary graft dysfunction after lung transplantation. Am J Transplant. 2013;13:1898–904.
16. Mach F. Statins as novel immunomodulators: from cell to potential clinical benefit. Thromb Haemost. 2003;90:607–10.
17. Sharma AK, Lapar DJ, Stone ML, Zhao Y, Metha CK, Kron IL, et al. NOX2 activation of natural killer T cells is blocked by the adenosine A2A receptor to inhibit lung ischemia-reperfusion injury. Am J Respir Crit Care Med. 2016;193:988–99.

Irene Bello[a,m,*,1,2], Alberto Sandiumenge[b,m], Elisabeth Coll[c], Mercedes de la Torre[d]

[a] *Thoracic Surgery and Lung Transplant Department, Vall d'Hebron Universitary Hospital, Barcelona, Spain*
[b] *Transplant Coordination Department, Vall d'Hebron Universitary Hospital, Barcelona, Spain*
[c] *Organización Nacional de Trasplantes, Madrid, Spain*
[d] *Thoracic Surgery, Complejo Hospitalario Universitario A Coruña, A Coruña, Spain*
[e] *Intensive Care Unit, Complejo Hospitalario Universitario A Coruña, A Coruña, Spain*
[f] *Thoracic Surgery, Hospital Marqués de Valdecillas, Santander, Spain*
[g] *Pneumology Department, Hospital Marqués de Valdecillas, Santander, Spain*
[h] *Intensive Care Unit, Hospital Marqués de Valdecillas, Santander, Spain*
[i] *Thoracic Surgery, Hospital Puerta de Hierro, Madrid, Spain*
[j] *Pneumology Department, Hospital Puerta de Hierro, Madrid, Spain*
[k] *Pneumology Department, Vall d'Hebron Universitary Hospital, Barcelona, Spain*
[l] *Intensive Care Unit, Vall d'Hebron Universitary Hospital, Barcelona, Spain*
[m] *Vall d'Hebron Institut de Recerca (VHIR), Barcelona, Spain*

* Corresponding author.
E-mail address: irbello@vhebron.net (I. Bello).
[1] https://twitter.com/@Dra_BelloIrene.
[2] https://twitter.com/@vallhebron.

https://doi.org/10.1016/j.arbres.2021.04.016

Tratamiento ambulatorio de la fuga aérea persistente

Outpatient Management of Persistent Air Leak

Estimado Director:

La fuga aérea es un problema frecuente en cirugía torácica, su prevalencia en el primer día postoperatorio es del 26-54%. Se considera fuga aérea persistente (FAP) postoperatoria si permanece el tercer día tras la cirugía según Brunelli[1], tras el cuarto según Cerfolio[2] y tras el quinto según Varela[3].

Más del 50% de los pacientes tratados mediante drenaje pleural (DP) por neumotórax (NX) presentan fuga aérea a las 48 horas[4]. La prevalencia de FAP varía entre el 8 y 20%, siendo más frecuente en NX espontáneos secundarios[5]. Se admite la utilización de dispositivos portátiles como la válvula de Heimlich (VH)[6] en aquellos pacientes con alto riesgo quirúrgico[7]. Con la VH se reduce el tiempo de drenaje y de hospitalización[5].

El objetivo de este estudio fue confirmar la inocuidad de la VH en pacientes con FAP postoperatoria y por NX, y demostrar su beneficio económico.

Se trata de un estudio descriptivo de una cohorte de pacientes con DP y VH por FAP al alta hospitalaria entre enero de 2013 y mayo de 2020, lo que determinó el tamaño muestral.

Se consideraron como criterios de inclusión a los pacientes con FAP tras NX o postoperados, estables, autónomos o con buen apoyo familiar. Como criterios de exclusión se consideraron la pérdida de seguimiento, las VH intrahospitalarias y las empleadas para diferir el tratamiento quirúrgico.

El seguimiento ambulatorio se realizó con revisiones cada 48-72 horas y el DP se retiró tras control radiológico después de 24 horas pinzado.

Las variables principales fueron la tasa de éxito, proporción de pacientes con resolución de la FAP tras colocar la VH y el coste ahorrado por tratamiento. Se estudiaron variables epidemiológicas, clínicas y radiológicas como variables independientes.

Se calculó la media, desviación típica y percentiles en las variables cuantitativas, frecuencia y porcentajes en las cualitativas. Se aplicó el test de Kolmogórov-Smirnov para comprobar la normalidad de los datos, la U de Mann-Whitney para comparar la distribución del tiempo entre dos grupos y el de Kruskall-Wallis en más de dos grupos. Se usó la regresión lineal múltiple con la técnica de los algoritmos genéticos para obtener el modelo más parsimonioso y la técnica de bootstrapping como método no paramétrico. Se empleó el test exacto de Fisher para comprobar la relación entre variables cualitativas.

La media de edad fue de 57 ± 17 años, el 73% varones. El 69% de los casos de FAP se produjeron tras cirugía torácica, el 34% fueron resecciones pulmonares mayores y el 48% menores. El 3% se produjo tras NX espontáneos primarios, el 26% tras NX secundarios y el 2% iatrogénicos, un total de 105 casos en 98 pacientes.

Los antecedentes pulmonares se muestran en la figura 1. El 30% presentaba un antecedente, otro 30% 2, el 14% 3, el 10% 4 y el 2% 5.

Las radiografías previas a la colocación de la VH mostraban el 64% una cámara aérea inferior al 20% y el 28% el pulmón completamente expandido. Tras la retirada del DP y VH un 36% presentaba una cámara aérea inferior al 10%, el 44% pulmones expandidos y NX completo en el 9,5%. Los pacientes han estado una media de 16 ± 8 días con DP y $7,5 \pm 5,2$ días con VH.

Tan solo el 7% de los casos presentó infección de la herida. Un total de 6 pacientes fueron reingresados, de los cuales 2 se resolvieron al conectar el drenaje a aspiración y 4 precisaron de nuevo DP (2 recibieron antibiótico por empiema pleural). Otros 8 pacientes fueron reintervenidos para resolver la FAP. En 2 pacientes se produjo la caída accidental del drenaje pleural.