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Role of mesenchymal stromal cells derivatives in diabetic foot ulcers: a controlled randomized phase 1/2 clinical trial

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Role of mesenchymal stromal cells derivatives in diabetic foot ulcers: a controlled randomized phase 1/2 clinical trial



Causa más común de morbilidad (entre diabéticos) y principal causa de amputación.



Regeneración de la piel



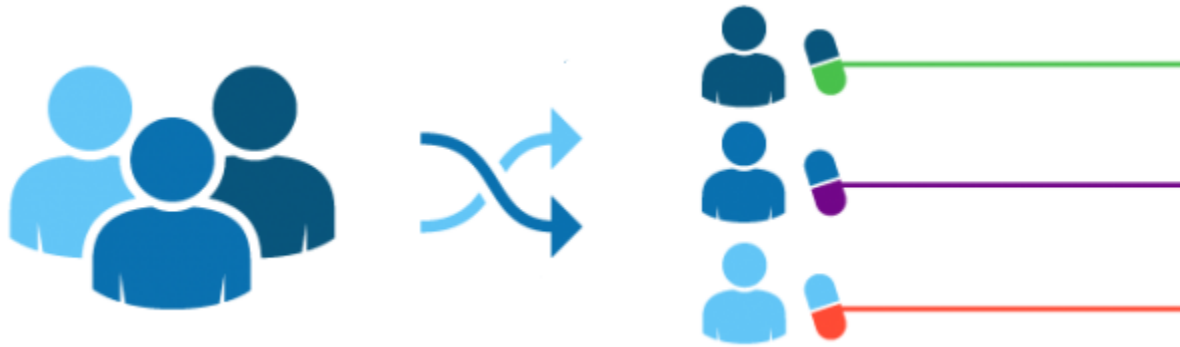
Enfermedad ulcerosa que no cicatriza.



Proof-of-concept: la administración de **derivados alogénicos de células estromales mesenquimales de médula ósea** (allo-hBM-MSCD) son efectivos en forma similar al uso de **células estromales mesenquimales de médula ósea alogénicas** (allo-hBM-MSD)



Role of mesenchymal stromal cells derivatives in diabetic foot ulcers: a controlled randomized phase 1/2 clinical trial



Ensayo clínico de grupos paralelos

Doble ciego

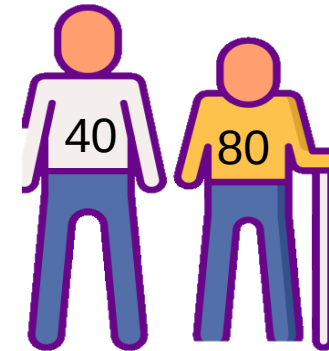
Controlado con placebo

Role of mesenchymal stromal cells derivatives in diabetic foot ulcers: a controlled randomized phase 1/2 clinical trial

Table 1
Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
• Adult male or female, 40 y of age or older (to 80 y old) • Diagnosis of diabetes • Presence of grade 1 or 2 DFUs • Surface area between 0.5 and 5.5 cm²	• Cancer • Presence of osteomyelitis • Diagnosis of brain or hematologic disorders • Use of immunosuppressive or cytotoxic drugs • Any acute systemic infectious disease process

DFU, diabetic foot ulcer.



Role of mesenchymal stromal cells derivatives in diabetic foot ulcers: a controlled randomized phase 1/2 clinical trial

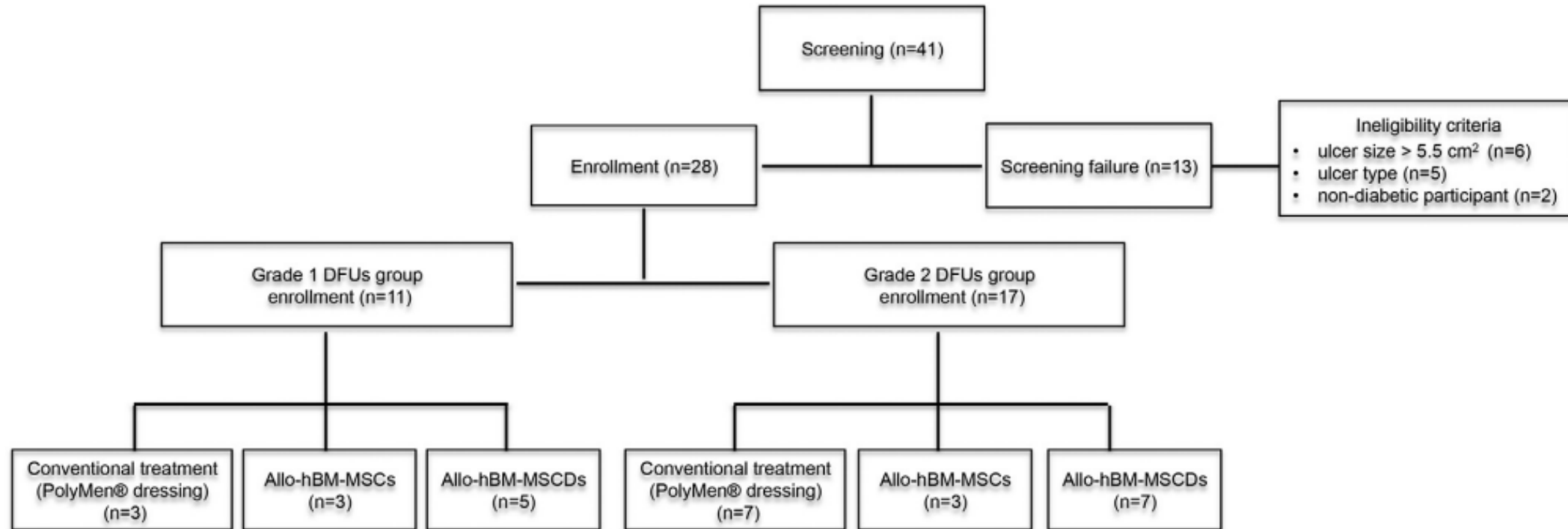
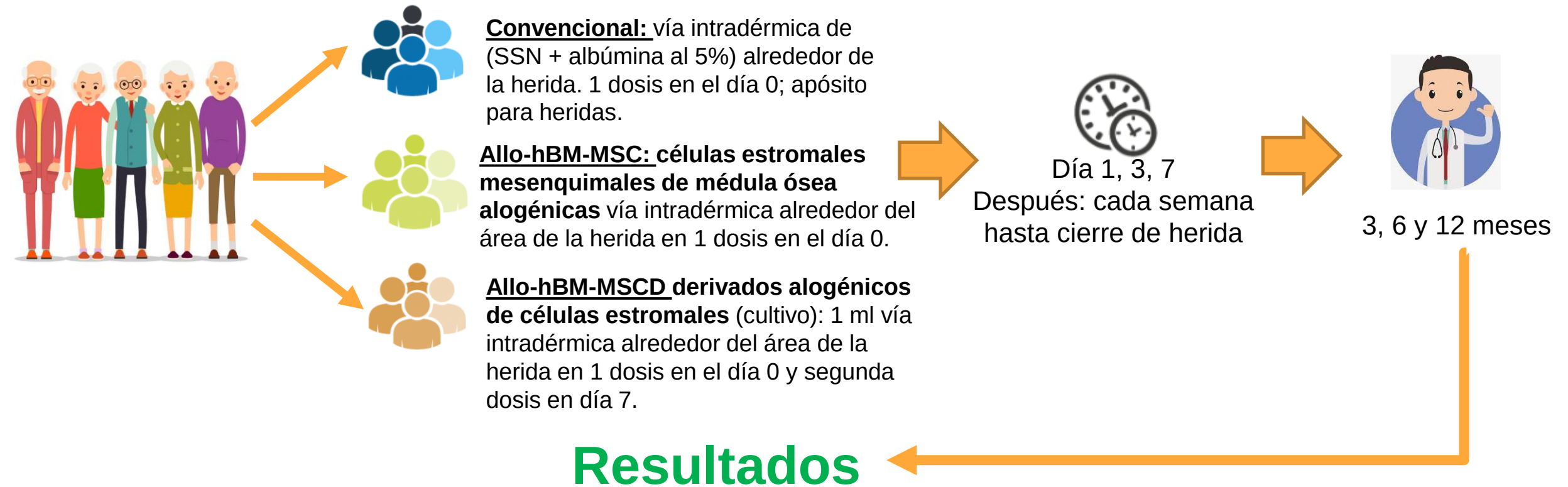


Figure 1. Participant flowchart. Reasons of screening failure: ulcer size $>5.5 \text{ cm}^2$ (6 participants), ulcer type (5 participants) and participant without diabetes (2 participants).

Allo-hBM-MSCD: Derivados alogénicos de células estromales mesenquimales de médula ósea

Allo-hBM-MSC: Células estromales mesenquimales de médula ósea alogénicas

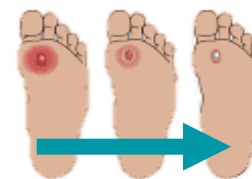
Role of mesenchymal stromal cells derivatives in diabetic foot ulcers: a controlled randomized phase 1/2 clinical trial



Seguridad:



Eficacia:



Role of mesenchymal stromal cells derivatives in diabetic foot ulcers: a controlled randomized phase 1/2 clinical trial

Table 2

Patient characteristics.

	Grade 1 DFUs			Grade 2 DFUs		
	Conventional treatment (PolyMem dressing)	Allo-hBM-MSCs	Allo-hBM-MSCDs	Conventional treatment (PolyMem dressing)	Allo-hBM-MSCs	Allo-hBM-MSCDs
Sex						
Male, n (%)	2 (67)	2 (67)	3 (60)	5 (71)	1 (33)	4 (57)
Female, n (%)	1 (33)	1 (33)	2 (40)	2 (29)	2 (66)	3 (43)
Age, y						
18-50 y, n (%)	0 (0)	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)
> 50 y, n (%)	3 (100)	2 (67)	5 (100)	7 (100)	3 (100)	7 (100)
Mean $\pm$ SD	59.67 $\pm$ 6.65	55.50 $\pm$ 13.44	65.80 $\pm$ 6.83	62.86 $\pm$ 8.45	63.33 $\pm$ 3.78	62 $\pm$ 8.12
Median	63	55.50	65	59	65	58
Min/max	52/64	46/65	57/74	55/77	59/66	54/74
Glycated hemoglobin A1c (%) at first and second month of study						
	Grade 1 DFUs		Grade 2 DFUs			
	First month	Second month	First month	Second month		
Mean $\pm$ SD	8.58 $\pm$ 2.48	9.48 $\pm$ 3.57	7.93 $\pm$ 1.13	7.52 $\pm$ 0.91		
Median	7.8	9.4	7.8	7.4		
Min/max	6.1 / 12.20	6.1 / 14	5.3 / 9.8	6.4 / 9.5		

Allo-hBM-MSCDs, allogeneic human bone marrow mesenchymal stromal cells derivatives; allo-hBM-MSCs, allogeneic human bone marrow mesenchymal stromal cells; DFUs, diabetic foot ulcer; SD, standard deviation.

Allo-hBM-MSCD: Derivados alogénicos de células estromales mesenquimales de médula ósea

Allo-hBM-MSC: Células estromales mesenquimales de médula ósea alogénicas

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Table 3

Wound baseline characteristics.

	Grade 1 DFUs			Grade 2 DFUs		
	Conventional treatment (PolyMem dressing)	Allo-hBM-MSCs	Allo-hBM-MSCDs	Conventional treatment (PolyMem dressing)	Allo-hBM-MSCs	Allo-hBM-MSCDs
Duration of ulcer, mo						
1 mo, <i>n</i>	0	0	0	3	0	2
2 mo, <i>n</i>	1	0	2	1	2	1
>2 mo, <i>n</i>	2	3	3	3	1	4
Mean $\pm$ SD	24.67 $\pm$ 23.01	21.50 $\pm$ 20.51	5.08 $\pm$ 4.26	2.14 $\pm$ 1.21	3.66 $\pm$ 2.88	6.28 $\pm$ 8.26
Median	24	21.5	5	2	2	2
Min/max	2/48	7/36	2/2	1/4	2/7	1/24
Initial wound area, cm ²						
Mean $\pm$ SD	0.80 $\pm$ 0.19	0.66 $\pm$ 0.31	0.53 $\pm$ 0.23	3.06 $\pm$ 1.38	3.59 $\pm$ 2.12	2.92 $\pm$ 1.26
Median	0.72	0.50	0.48	2.77	4.42	2.83
Min/max	0.66 / 1.03	0.46/1.02	0.35/0.92	1.65/5.60	1.17/5.17	1.25/5.30
Ulcer location, <i>n</i> (%)						
Foot right (plantar)	3 (100)	2 (66)	4 (80)	5 (71.4)	1 (34)	3 (42.8)
Foot left (plantar)	0 (0)	1 (34)	1 (20)	2 (28.6)	2 (66)	4 (57.2)

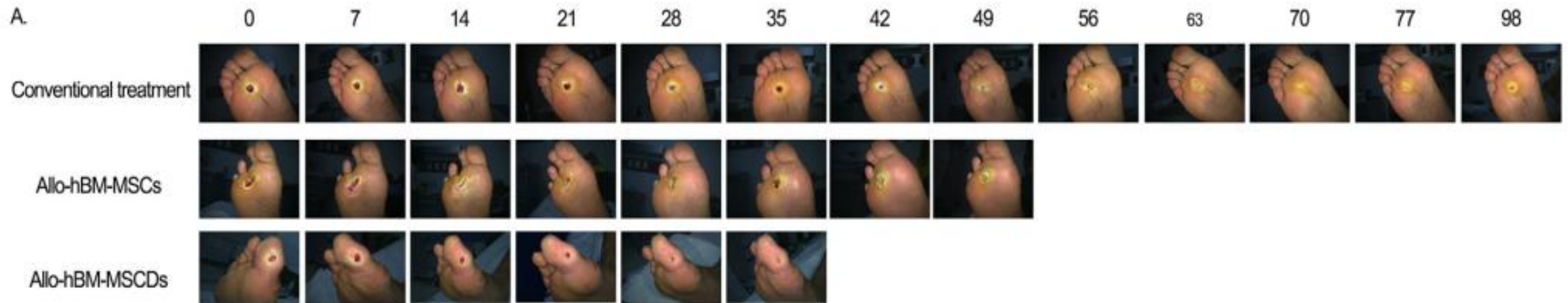
Allo-hBM-MSCDs, allogeneic human bone marrow mesenchymal stromal cells derivatives; allo-hBM-MSCs, allogeneic human bone marrow mesenchymal stromal cells; DFUs, diabetic foot ulcer; SD, standard deviation.

Allo-hBM-MSCD: **Derivados alogénicos de células estromales mesenquimales de médula ósea**

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Role of mesenchymal stromal cells derivatives in diabetic foot ulcers: a controlled randomized phase 1/2 clinical trial

Evolución de la progresión de la cicatrización de heridas hasta el cierre (UPD 1).

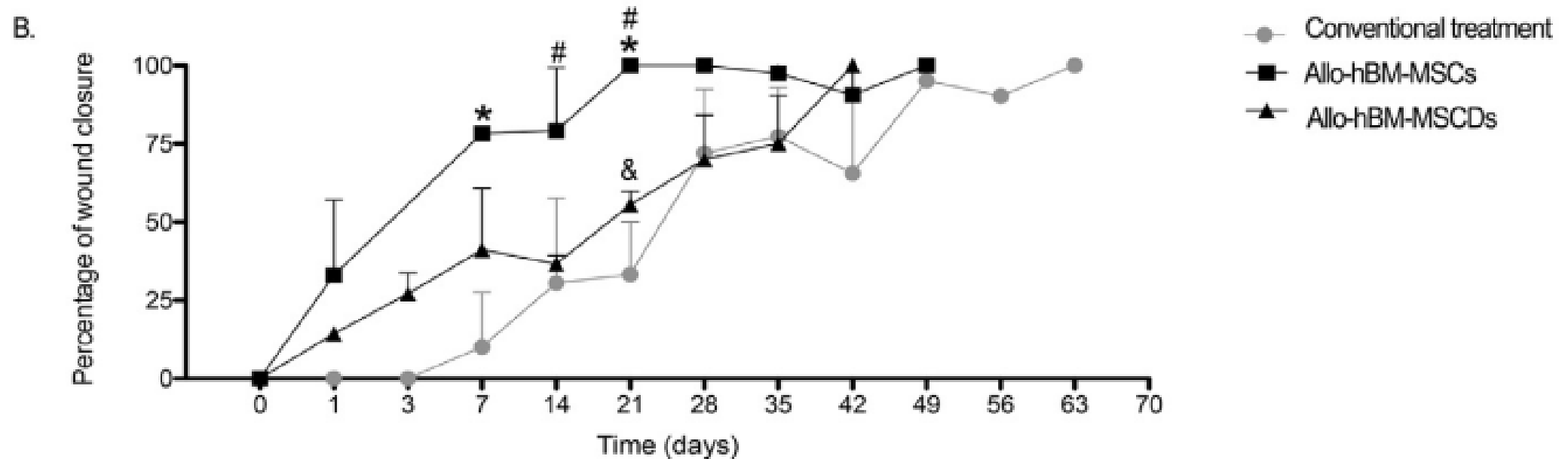


Allo-hBM-MSCD: Derivados alogénicos de células estromales mesenquimales de médula ósea

Allo-hBM-MSC: Células estromales mesenquimales de médula ósea alogénicas

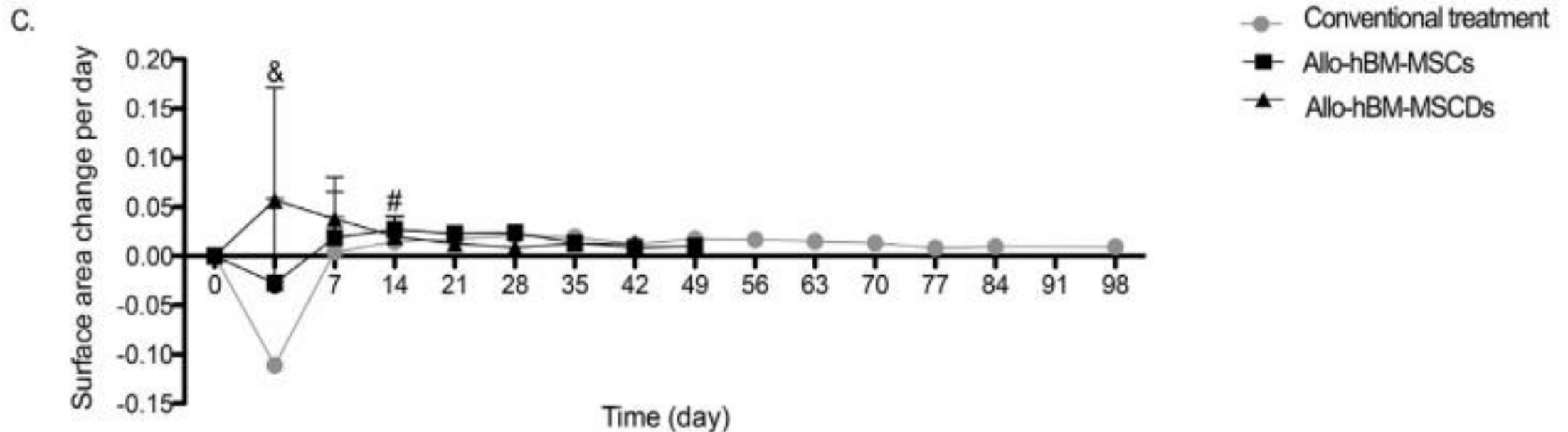
Role of mesenchymal stromal cells derivatives in diabetic foot ulcers: a controlled randomized phase 1/2 clinical trial

Diferencias significativas entre: **allo-hBM-MSC** (células estromales mesenquimales de médula ósea alogénicas) versus enfoque convencional (*), **allo-hBM-MSCD** (derivados alogénicos de células estromales mesenquimales de médula ósea) versus enfoque convencional (&), alo-hBM-MSC versus hBM-MSCD (#).



Role of mesenchymal stromal cells derivatives in diabetic foot ulcers: a controlled randomized phase 1/2 clinical trial

Diferencias significativas entre: **allo-hBM-MSC** (células estromales mesenquimales de médula ósea alogénicas) versus enfoque convencional (*), **allo-hBM-MSCD** (derivados alogénicos de células estromales mesenquimales de médula ósea) versus enfoque convencional (&), alo-hBM-MSC versus hBM-MSCD (#).



Role of mesenchymal stromal cells derivatives in diabetic foot ulcers: a controlled randomized phase 1/2 clinical trial

Evolución de la progresión de la cicatrización de heridas hasta el cierre (UPD 2).

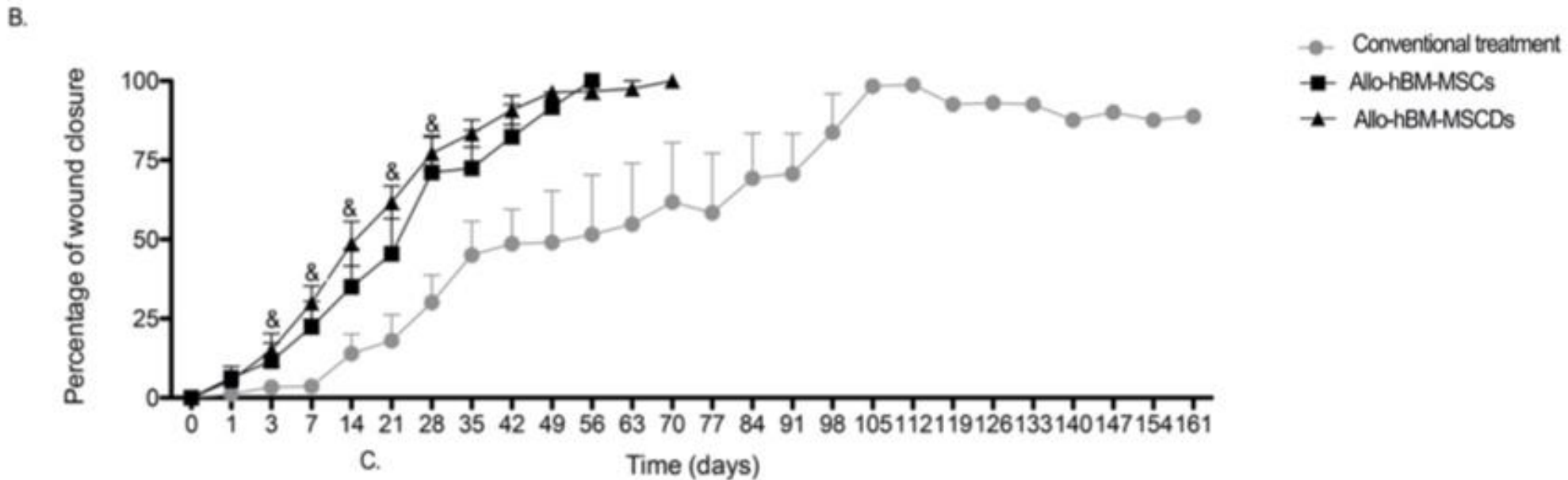


Allo-hBM-MSCD: **Derivados alogénicos de células estromales mesenquimales de médula ósea**

Allo-hBM-MSC: **Células estromales mesenquimales de médula ósea alogénicas**

Role of mesenchymal stromal cells derivatives in diabetic foot ulcers: a controlled randomized phase 1/2 clinical trial

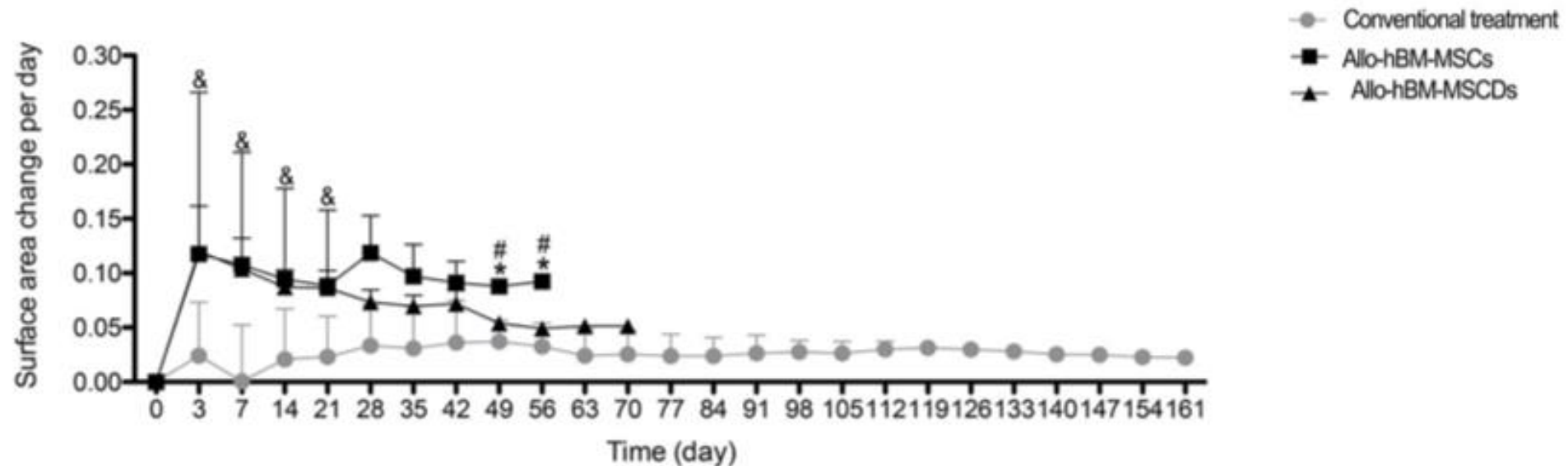
Diferencias significativas entre: **allo-hBM-MSC** (células estromales mesenquimales de médula ósea alogénicas) versus enfoque convencional (*), **allo-hBM-MSCD** (derivados alogénicos de células estromales mesenquimales de médula ósea) versus enfoque convencional (&), alo-hBM-MSC versus hBM-MSCD (#).



Role of mesenchymal stromal cells derivatives in diabetic foot ulcers: a controlled randomized phase 1/2 clinical trial

Diferencias significativas entre: **allo-hBM-MSC** (células estromales mesenquimales de médula ósea alogénicas) versus enfoque convencional (*), **allo-hBM-MSCD** (derivados alogénicos de células estromales mesenquimales de médula ósea) versus enfoque convencional (&), alo-hBM-MSC versus hBM-MSCD (#).

C.



Role of mesenchymal stromal cells derivatives in diabetic foot ulcers: a controlled randomized phase 1/2 clinical trial

Percentage reduction in wound perimeter.

Time, wk	Grade 1 DFUs			Grade 2 DFUs		
	Conventional treatment (PolyMem dressing) versus Allo-hBM-MSCs	Conventional treatment (PolyMem dressing) versus Allo-hBM-MSCDs	Allo-hBM-MSCs versus Allo-hBM-MSCDs	Conventional treatment (PolyMem dressing) versus Allo-hBM-MSCs	Conventional treatment (PolyMem dressing) versus Allo-hBM-MSCDs	Allo-hBM-MSCs versus Allo-hBM-MSCDs
1	0.3600 (NS)	0.5204 (NS)	0.1139 (NS)	0.0357 (*)	0.0087 (**)	0.2619 (NS)
2	0.1907 (NS)	0.4547 (NS)	0.9819 (NS)	0.1954 (NS)	0.0476 (*)	0.7528 (NS)
3	0.0233 (*)	0.5311 (NS)	0.3403 (NS)	0.1084 (NS)	0.0139 (*)	0.6359 (NS)
4	0.0451 (*)	0.3267 (NS)	0.7294 (NS)	0.0358 (*)	0.0057 (**)	0.0667 (NS)
5	0.0121 (*)	0.5162 (NS)	0.6668 (NS)	0.0357 (*)	0.0025 (*)	0.1167 (NS)
6	0.2074 (NS)	0.2229 (NS)	0.2254 (NS)	0.0509 (NS)	0.0043 (**)	0.2911 (NS)
7	0.2254 (NS)	0.2254 (NS)	0.2254 (NS)	0.0819 (NS)	0.0095 (**)	0.0932 (NS)

Allo-hBM-MSCDs, allogeneic human bone marrow mesenchymal stromal cells derivatives; allo-hBM-MSCs, allogeneic human bone marrow mesenchymal stromal cells; DFUs, diabetic foot ulcer; NS, not significant.

(*) (**) statistical significance

Allo-hBM-MSCD: **Derivados alogénicos de células estromales mesenquimales de médula ósea**

Allo-hBM-MSC: **Células estromales mesenquimales de médula ósea alogénicas**

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Table 5

Hazard ratios and healing rate (person/day).

Variable	Closure rate at 50%				Closure rate at 100%			
	HRs	CI	P value	Healing rate (person/day)	HRs	CI	P value	Healing rate (person/day)
Age	0.989	0.937–1.043	0.688	NA	0.995	0.941–1.052	0.868	NA
Female	1.206	0.532–2.734	0.653	NA	0.850	0.362–1.990	0.708	NA
HbA1c	1.166	0.884–1.539	0.276	NA	1.038	0.796–1.354	0.779	NA
Closing rate according to DFUs type								
Grade 1				0.0647				0.025
Grade 2	2.468	1.040–5.853	0.04	0.0318	2.844	1.218–6.638	0.016	0.010
Treatment								
Conventional treatment (PolyMen dressing)				0.022				0.005
Allo-hBM-MSCs	9.921	2.390–41.182	0.002 *	0.078	7.795	1.891–32.135	0.004 *	0.025
Allo-hBM-MSCDs	9.132	2.175–38.335	0.003 *	0.062	10.085	2.668–38.112	0.001 *	0.025

Allo-hBM-MSCDs, allogeneic human bone marrow mesenchymal stromal cells derivatives; allo-hBM-MSCs, allogeneic human bone marrow mesenchymal stromal cells; CI, confidence interval; DFUs, diabetic foot ulcer; HRs, hazard ratios; NA, not applicable.

(*) statistical significance

Allo-hBM-MSCD: Derivados alogénicos de células estromales mesenquimales de médula ósea

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