Evaluation of a marine Oxygen carrier (HEMO$_2$life®) for organ preservation: first use in kidney transplantation in humans

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BACKGROUND

Today, awaiting transplant surgery, kidney grafts are preserved at 4° C to reduce the enzymatic activity, either in static conditions or on a machine perfusion. Preservation solutions are aimed to reduce damages associated with ischemia/reperfusion injuries (IRIs). To date none of them really prevents injuries due to hypoxia and reoxygenation. These injuries have deleterious effects on long term graft survival.

The Medical Device HEMO$_2$life® is a natural extracellular hemoglobin (Hb) isolated from the marine lugworm *Arenicola marina*. This biopolymer of high molecular weight (~3,600 kDa) composed of 156 globin and 44 non-globin linker chains has a large oxygen binding capacity, carrying up to 156 oxygen molecules when saturated (in comparison to 4 for human Hb). It releases oxygen according to a simple gradient without requiring any allosteric effector.

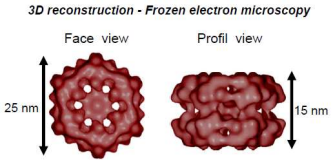


Figure 1: Structure of the extracellular hemoglobin (M101)

Figure 2: Glass vial containing 1g of HEMO$_2$life® solution (20mL)

Figure 3: HEMO$_2$life® once injected in a preservation solution bag.

HEMO$_2$life® CE mark on-going. This Medical Device is not yet commercialized.

OBJECTIVES

This is a multicenter safety study evaluating for the first time in humans the use of an oxygen carrier HEMO$_2$life® as an additive in organ preservation solution in kidney transplantation. The primary end point was a safety endpoint analyzed by collecting all events within the first 3 months in terms of HEMO$_2$life® adverse events, graft safety and recipient safety. Efficacy was evaluated as a secondary endpoint: comparison of both groups at 3 months and 1 year; comparison of HEMO$_2$life group® with an historical cohort and histological evaluation.

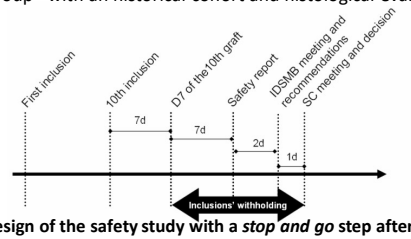
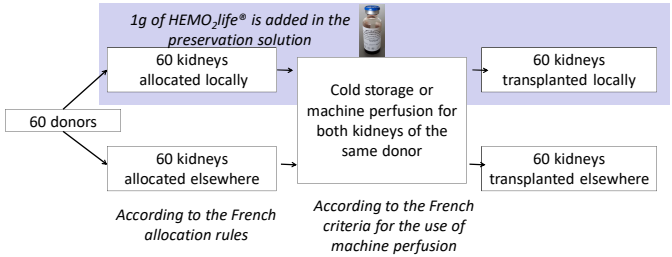


Figure 4: Design of the safety study with a *stop and go* step after 10 inclusions

METHODS

This was a national multicentric open-labeled safety study on a medical device. The study planed to include 60 grafts from deceased donors after brain death, retrieved and transplanted locally within the 6 participating centers.



Organ perfusion: The same perfusion solution was used in the 6 transplant centers: the Cold Storage Solution Belzer UW®.

HEMO$_2$life® use: For cold storage, the kidney was perfused on the backtable and transferred to the storage container with a solution of Belzer UW ® + HEMO$_2$life® (1g per liter). For machine-perfused grafts, 1g HEMO$_2$life® was added to 1 liter of Machine Perfusion Solution Belzer UW®.

RESULTS: donors and recipients

As no issue appeared in the *stop and go* phase, 60 graft kidneys from 60 deceased donors were preserved in a solution containing HEMO$_2$life®. Among them, 2 kidney grafts were not transplanted due to macroscopic lesions of the graft and surgeon decision.

	Donors n= 58	Recipients n=58
Age, years (median +/- SD)	50.34 +/- 16.09	51.64 +/- 13.6
Male, %	30 (51.7)	39 (67.2)
ECD donors, %	23 (38)	
Use of machine perfusion, %	21 (36.84)	
Preemptive transplantation, %		7 (12.1)

RESULTS: 3-month safety

RESULT 1: According to the IDSMB conclusions it was confirmed that the use of HEMO$_2$life® in preservation solution is safe for the patient and for the graft.

	Recipients (57)	
Death	0	
Graft loss	2	← *Not related to the product (IDSMB)*
DGF (= at least one HD session) (%)	14 (24.1)	} *Not superior than an historical population*
Acute rejection, %	2 (3.4)	

At 3-month, 25 SAE were reported including: 2 graft losses, 4 infections (2 pyelonephritis, 1 orchitis, 1 klebsellia sepsis), 2 acute rejections, 4 cardiac events , 11 various graft complications.

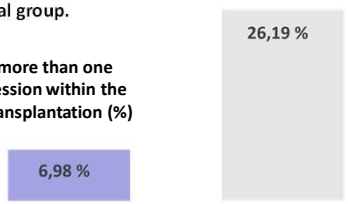
RESULTS: 3-month efficacy

For the efficacy secondary end points we performed a paired analysis comparing the grafts receiving HEMO$_2$life® and their contralateral kidney after exclusion of the pairs with at least one recipient being transplanted preemptively. Patient and graft survival were comparable in the 2 groups.

	HEMO$_2$life® n= 43	Contralateral n=43
Age, years (mean +/- SD)	51.32 +/- 13.49	49.54 +/- 12.89
Male (%)	38 (66.67)	33 (57.89)
Use of machine perfusion (%)	21 (36.84)	20 (35.09)
Cold ischemia time (min)	741 +/- 260	1054 +/- 349

RESULT 2: The HEMO$_2$life® group presented less delayed graft function than the contralateral group.

Figure 5: DGF = more than one HemoDialysis session within the 1st week post transplantation (%)



	HEMO$_2$life® n= 43	Contralateral n=43	p
DGF: at least one HD session (%)	10 (23.26)	14 (32.56)	0,4544

RESULT 3: Recovery of renal function in the first month was better in the HEMO$_2$life® group as compared with the contralateral kidneys.

	HEMO$_2$life® n= 43	Contralateral n=43	p
Days for creatinine < 250 µmol	6.93 +/- 9.16	13.17 +/- 13.83	0.0208
AUC of creatinine D1 to D7	1709+/- 873	2717+/- 1878	0.042

In the univariate analysis, cold ischemia time and patient group (HEMO$_2$life® versus contralateral) were significantly related to DGF and renal function. This effect disappeared for both variables in the multivariate analysis.

Further analysis are still on going: 1-year follow-up, comparison of HEMO$_2$life® group vs historical cohort, histological evaluation.

CONCLUSIONS

The 3-month analysis of the study showed that the safety primary end point was met. Even if the study was not designed to show superiority of HEMO$_2$life® the secondary efficacy end points were all in favor (delayed graft function and renal function) of the HEMO$_2$life® group when compared with the contralateral group.

In this context, the next step will be to design a prospective randomized study evaluating the efficacy of HEMO$_2$life® in a larger cohort of patients.