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Heparin Conjugate Pretreatment of Kidneys From Deceased Donors Before Transplantation: Results From the First-in-human Randomized Phase I Trial

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Background. Pretreating porcine kidneys with Corline Heparin Conjugate (CHC) during hypothermic machine perfusion (HMP) has been shown to reduce preservation injury and improve early kidney function. In this first-in-human phase I study, the safety and tolerability of transplanting CHC-pretreated kidneys were evaluated. **Methods.** CHC or placebo was added to the preservation solution during HMP of donated kidneys from deceased donors for at least 3 h before transplantation into adult patients. The primary safety endpoint was the number and severity of adverse events (AEs) and serious AEs (SAEs) during the first 30 d after transplantation. **Results.** In the first 30 d, 66 AEs were reported in 8 patients who received CHC-pretreated kidneys with 39 AEs in 8 patients who received placebo-pretreated kidneys ($P = 0.1$ in post hoc analysis). The most common AEs were hypertension (CHC, n = 5; placebo, n = 2) and anemia (CHC, n = 5; placebo, n = 2). Most AEs were assessed as mild (58%) or moderate (39%) and not related to treatment (95%). There were 2 SAEs reported in each group. One SAE, considered possibly related to CHC treatment, was a case of severe postprocedural hemorrhage that required reoperation. No patients needed dialysis. There were no observed rejections and no patient deaths. **Conclusions.** Pretreatment of kidneys with CHC before transplantation was considered safe and tolerable. Efficacy studies are now planned to investigate if CHC can reduce early ischemia-reperfusion injury in humans.

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INTRODUCTION

Ischemia-reperfusion injury (IRI) leading to delayed graft function (DGF) may significantly affect outcomes, including immediate and 12-mo function and graft survival after kidney transplantation.[1-3] There is now good evidence that hypothermic machine perfusion (HMP), with or without oxygen, can reduce the risk of DGF and improve graft survival compared with static cold storage using donor kidneys from standard and older and higher risk donors.[4-7]

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A.S. was the coordinating and principal investigator of the study and, along with T.Lo., participated in developing the idea, designing the study, and results interpretation. T.Lu., P.L., J.N. were also involved in the clinical conduct of the study. F.C., P.M., R.P., and J.J. were involved in main and exploratory endpoint analyses. All authors contributed to the article review and approved the final version of the article.

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Furthermore, HMP provides additional information on kidney viability and quality and may offer the opportunity for kidney repair.

An important target in the complex pathophysiological processes of IRI is the endothelial glycocalyx, which is a thin layer that provides the interface between blood and endothelium and helps maintain proper control of hemostasis and inflammation.[8,9] Proteoglycans and glycoproteins make up the backbone of the endothelial glycocalyx, whereas attached glycosaminoglycans (eg, heparin and chondroitin sulfate) form a matrix with plasma components such as albumin. Destruction of the endothelial glycocalyx has been observed in lung and kidney grafts during ischemic organ preservation.[10] Also, the extent of glycocalyx damage was found to correlate with cellular injury severity after liver transplantation.[10] Enhanced protection of the renal endothelial glycocalyx might maintain the properties of the vascular endothelium and lead to an improved renal function early after transplantation.

Corline Heparin Conjugate (CHC; Corline Biomedical AB, Uppsala, Sweden) consists of multiple (>20) unfractionated heparin chains that are linked by covalent bonds to a straight chain of aliphatic amines without compromising heparin binding sites for antithrombin.[11] CHC bound to endothelium reduces inflammation and inhibits activation of thrombosis in preclinical models.[9,12,13] It has also been shown that CHC may be used to coat the vessel walls of perfused porcine kidneys during HMP.[14] Subsequently, we demonstrated in the pig model that perfusion of kidneys with CHC during HMP reduced preservation injury and improved early kidney function, demonstrating a significantly faster reduction of creatinine levels, larger total urinary volumes, less tubular changes, and lower intrarenal resistance with no evidence of altered clotting.[15]

Therefore, in this first-in-human phase I study, we aimed to evaluate the safety and tolerability of CHC pretreatment of kidneys from deceased donors before transplantation.

MATERIALS AND METHODS

Study Design

The study was a first-in-human randomized, double-blind, placebo-controlled phase I study performed at 3 Swedish clinical sites (Uppsala University Hospital, Karolinska University Hospital, and Sahlgrenska University Hospital). The study was conducted in accordance with the Declaration of Helsinki and with the International Conference on Harmonization Guideline for Good Clinical Practice E6 (R2), the European Union Clinical Trials Directive, and applicable local regulatory requirements. The protocol was approved by the Swedish ethical review authority and by the Swedish Medical Products Agency. All patients gave written informed consent before study enrollment. The first patient was screened on February 14, 2019, and the last patient completed on April 21, 2020.

Study Participants

Eligible study participants were male and female patients aged 18 to 75 y who were listed for kidney transplantation obtained from a deceased donor at the 3 clinical sites mentioned above. Only patients waiting for their first or second transplantation were eligible. A negative crossmatch test before transplantation was required, without the presence of donor-specific antibodies.

Exclusion criteria included patients at increased risk of thrombosis or bleeding (international normalization ratio >1.5), anticoagulant treatment with warfarin for an indication unrelated to the kidney transplantation, and a history of heparin-induced thrombocytopenia. Patients were also excluded if there was electrocardiogram (ECG)-based evidence of acute myocardial infarction, unstable angina, decompensated heart failure, third degree of heart block, or cardiac arrhythmia associated with hemodynamic stability.

Donor kidneys were placed on HMP using a LifePort kidney transporter at the retrieval hospital. For study inclusion, transplanted kidneys had to come from deceased donors older than 18 y of age who had not died because of a circulatory arrest. Organs were excluded if they had not been adequately perfused because of technical failure during HMP. The regular protocols for organ donation according to Swedish law were followed. Donor details recorded were age, cause of death (if available), and organ quality (expanded criteria donors [ECDs] yes/no). ECD was defined as all donors >60 y or donors >50 y with any 2 of the following: hypertension; cerebrovascular cause of brain death; or preretrieval serum creatinine level >1.5 mg/dL (132 μmol/L).

Randomization and Interventions

Eligible and consenting patients were randomized to 1 of 2 study arms: CHC or placebo (visit 1). Randomization was performed using a block design and a randomization code list created per site. Site staff, patients, surgeons, coordinators, and the sponsor were all blinded to treatment allocation. Based on porcine kidney studies[15] and the larger size of human kidneys, a fixed single ex vivo dose of CHC 100 mg was chosen. The CHC dose was diluted to 2 mg/mL with Belzer MPS (Belzer Machine Perfusion Solution). Placebo consisted of Belzer MPS solution only. When the clinic was informed about the imminent transplantation, the investigator or research nurse contacted the pharmacy with a request to prepare the investigational medicinal product (IMP), CHC, or placebo, according to the randomization list and separate instructions. A requirement for addition of IMP at the implanting hospital was optimal function of HMP during transport, without signs of leakage at the connection point and other abnormalities.

The IMP was added to the preservation solution during HMP of the kidney at least 3 h before transplantation. Just before removal of the kidney for transplantation, perfusion fluids were analyzed for the remaining CHC, and CHC uptake by the kidney was indirectly calculated as described previously.[15] When the kidney was taken out of the LifePort transporter, it was flushed with at least 300 mL pure Belzer MPS before transplantation, removing any soluble CHC.

The kidney was transplanted to the recipient using standard surgical procedures. Patients were hospitalized for at least 7 d after transplantation as per clinical routine. Study visits took place at transplant (visit 1), after 1 d ± 6 h (visit 2), 2 d ± 12 h (visit 3), 4 d ± 1 d (visit 4), and 7 d ± 2 d (visit 5). After discharge, all recipients visited the outpatient clinic at 14 d ± 4 d (visit 6) and 30 d ± 4 d (visit 7) posttransplantation for safety and follow-up assessments. Patients then continued to be followed up in accordance with normal clinical practice after this time, beyond the scope of this report.

Primary and Secondary Endpoints

The primary safety endpoint was the number and severity grade of serious adverse events (SAEs) and adverse events (AEs), including a description of their associated Medical Dictionary for Regulatory Activities terms (version 21.0), during the first 30 d after transplantation. Secondary safety endpoints were the proportion of patients requiring dialysis for any reason in the first 7 d posttransplant (definition of DGF); the incidence of dialysis initiation 8 to 30 d posttransplantation; bleeding volume during the primary operation; the total number of bleeding events and bleeding severity related to the kidney transplantation in the first 48 h; and the frequency of reoperation because of bleeding after the primary operation and up to 30 d. Postoperative bleeding was defined as a >25 g/L decrease in hemoglobin (Hb) concentration compared with the 1-h postoperative Hb value, and if the threshold value was exceeded, a computed tomography scan was performed to confirm bleeding (versus hemodilution). Vital signs and laboratory parameters were regularly checked, and ECGs and physical examinations were performed before and several times after transplantation.

Tertiary Endpoints

Tertiary endpoints related to kidney function included change from baseline in serum creatinine, serum cystatin C, and estimated glomerular filtration (eGFR) using the modification of diet in renal disease (MDRD, 4-parameter) formula at various timepoints.

Uptake of CHC in the donor kidney was assessed indirectly by measuring CHC levels in samples of perfusion solution after removal of the kidney from the perfusion machine.

Statistical Analysis

No formal sample size calculation was performed. It was planned to randomize 18 patients, 9 to each treatment arm; however, in the interest of patient safety because of the COVID-19 pandemic, the sponsor decided to discontinue further recruitment on March 30, 2020, after enrollment of 16 patients. This sample size was considered sufficient to provide adequate information for the study's primary objective. Data are expressed as mean ± SD or median (minimum, maximum).

Before database closure, the statistical plan was amended to include statistical testing of some of the secondary endpoints. The paired Student *t* test was used to compare numerical parameters of the recipients. The Fisher exact test was used to compare the need for dialysis and the number of bleeding events between groups, whereas the Wilcoxon rank sum test was used to compare estimated bleeding volume during the operation. In a post hoc analysis, the number of AEs was compared between the 2 groups with the Wilcoxon rank sum test.

RESULTS

Of the 17 patients screened for participation, 16 were eligible for inclusion. All eligible patients were randomized, 8 to each study arm (CHC or placebo). Summary demographic data on the 16 enrolled patients are provided in Table 1. All randomized patients completed the study procedures. There were 42 protocol deviations in 15 patients; 3 were classified as major deviations, but they did not exclude the patients from the full analysis set population. One patient in the placebo group had some safety laboratory parameters missing at baseline and signed the incorrect version of the patient information form at inclusion, with the correct version signed retrospectively. One patient in the CHC group had data missing on alkaline phosphatase at baseline. The total time in the study was 243 d in the CHC group and 234 d in the placebo group.

The baseline characteristics of the recipients and donors differed to some extent between the 2 groups. The mean ± SD age of the patients was 54.3 ± 10.1 y in the CHC group and 60.3 ± 8.1 y in the placebo group. BMI at screening was 29.0 ± 3.6 kg/m^2 in the CHC group and 22.5 ± 3.9 kg/m^2 in the placebo group; post hoc analysis indicated a significant difference in BMI between the groups ($P = 0.005$). Donors were aged 53 ± 14 y and 69 ± 8 y in the CHC and placebo groups ($P = 0.02$), respectively, whereas 5 of 8 kidneys in the CHC group were from ECDs compared with 7 of 8 in the placebo group.

There was no statistically significant difference in mean organ weight (after flush-out) in the CHC and placebo groups (267 ± 51 g versus 240 ± 35 g, respectively). The total mean cold ischemia time was 15 ± 4 h with CHC and 17 ± 4 h with placebo. There was also no difference in mean exposure time to the IMP (7.8 ± 3.8 h with CHC and 7.0 ± 3.5 h with placebo).

Primary Endpoint

The total number of AEs reported in the first 30 d after transplantation was 66 in the CHC groups and 39 in the placebo (Table 2), with no statistically significance between the groups in a post hoc analysis ($P = 0.1$). The most commonly reported AEs were hypertension (CHC, n = 5; placebo, n = 2); anemia (CHC, n = 5; placebo, n = 2), urinary tract infection (CHC, n = 1; placebo, n = 4), and hyperkalemia/blood potassium increased (CHC, n = 4; placebo, n = 1) (Table S1, SDC, http://links.lww.com/TXD/A471).

Most AEs were assessed as mild (58%) or moderate (39%) and not related to study treatment (95%). Four AEs were considered possibly related to study treatment in the CHC group (Table S1, SDC, http://links.lww.com/TXD/A471). Three of these AEs (anemia and 2 events of hematoma) occurred in the same patient, whereas the other event was an SAE of postprocedural hemorrhage, which led to reoperation. Although the possibility that the SAE was because of CHC cannot be ruled out, all other recipients of other organs from the same donor experienced similar bleeding problems. One AE, oral fungal infection, was considered possibly related to IMP in the placebo group, with no AEs assessed as probably related to study treatment.

In addition to the SAE of severe postprocedural hemorrhage, 1 further SAE was reported in the CHC group (urosepsis), which was not considered related to study treatment (Table S1, SDC, http://links.lww.com/TXD/A471). Two SAEs in the placebo group (urosepsis and urinary retention) were not considered related to study treatment. There were no deaths, no AEs that led to withdrawal, and no observed signs of rejection.

Secondary Endpoints

Regarding clinical safety endpoints, no patients required dialysis. Median (min, max) volume of bleeding during the operation was 200 (100, 800) mL in the CHC group and 65 (50, 350) mL in the placebo group, which was significant in a post hoc analysis ($P = 0.03$). One patient in the CHC group

TABLE 1.

Baseline demographics and characteristics of the recipients

	CHC (n = 8)	Placebo (n = 8)	*P*
Age, y			0.21[a]
Mean (SD)	54.3 (10.1)	60.3 (8.1)	
Median (min, max)	51.0 (41, 73)	58.5 (47, 73)	
Height, cm			0.31[a]
Mean (SD)	176.8 (9.0)	172.1 (8.6)	
Median (min, max)	179.0 (161, 188)	172.5 (156, 183)	
Weight, kg			0.0126[a]
Mean (SD)	90.8 (15.9)	67.4 (16.8)	
Median (min, max)	88.1 (73, 114)	71.8 (46, 92)	
Body mass index, kg/m^2			0.0037[a]
Mean (SD)	29.0 (3.6)	22.5 (3.9)	
Median (min, max)	28.1 (24, 35)	23.1 (17, 28)	
Sex, n (%)			0.61[b]
Female	2 (25)	4 (50)	
Male	6 (75)	4 (50)	
Dialysis, n (%)	4 (50)	5 (63)	1[b]
Hemodialysis, n (%)	2 (25)	1 (13)	1[b]
Peritoneal dialysis, n (%)	1 (13)	2 (25)	1[b]
Previous renal transplant, n (%)	1 (13)	2 (25)	1[b]
End-stage renal disease, n (%)	1 (13)	2 (25)	1[b]
Diabetic nephropathy, n (%)	0	2 (25)	0.47[b]
Anemia, n (%)	4 (50)	4 (50)	1[b]
Hypertension, n (%)	5 (63)	7 (88)	0.57[b]

[a]Paired Student *t* test.
[b]Fisher exact test.
CHC, Corline Heparin Conjugate.

TABLE 2.

Overview of AEs

	CHC (n = 8)		Placebo (n = 8)	
	Number of patients (%)	Number of events	Number of patients (%)	Number of events
Any AE	8 (100)	66[a]	8 (100)	39[a]
Any SAE	2 (25)	2	2 (25)	2
Any AE leading to withdrawal	0	0	0	0
Any AE leading to death	0	0	0	0
Causality				
Not related	8 (100)	62	8 (100)	38
Possibly	2 (25)	4	1 (13)	1
Probably	0	0	0	0
Severity				
Mild	7 (88)	39	7 (88)	22
Moderate	6 (75)	25	6 (75)	16
Severe	2 (25)	2	1 (13)	1

[a]No statistical significance between the groups in a post hoc analysis ($P = 0.1$).
AE, adverse event; CHC, Corline Heparin Conjugate; SAE, serious AE.

bled 800 mL. In a separate patient, there was 1 occurrence of postoperative bleeding and reoperation, which is the SAE of severe postprocedural hemorrhage mentioned above. There were no differences between the groups for vital signs, ECG, and clinical and physical examination. One of the abnormal safety laboratory values related to an AE, a reduction in Hb (from 133 g/L at screening to 84–86 g/L at visits 4–6), was assessed as possibly related to CHC.

Based on post hoc analyses, there were no significant differences between the groups in the proportion of laboratory values reported as abnormal.

Tertiary Endpoints

Significant numerical differences between groups in laboratory mean values were reported for serum creatinine (higher with CHC at visits 4–7), serum cystatin C (higher with CHC at Visits 3–6), and eGFR values calculated using the MDRD formula (lower with CHC at visits 3–5) ($P \leq 0.05$) (Figure 1).

When CHC uptake was indirectly measured, between 21 mg and 52 mg of the administered CHC was retained in the kidneys (Table S2, SDC, http://links.lww.com/TXD/A471). CHC uptake per 100 g of kidney weight was 8 to 14 mg, with a single kidney having a higher uptake (31 mg/100 g).

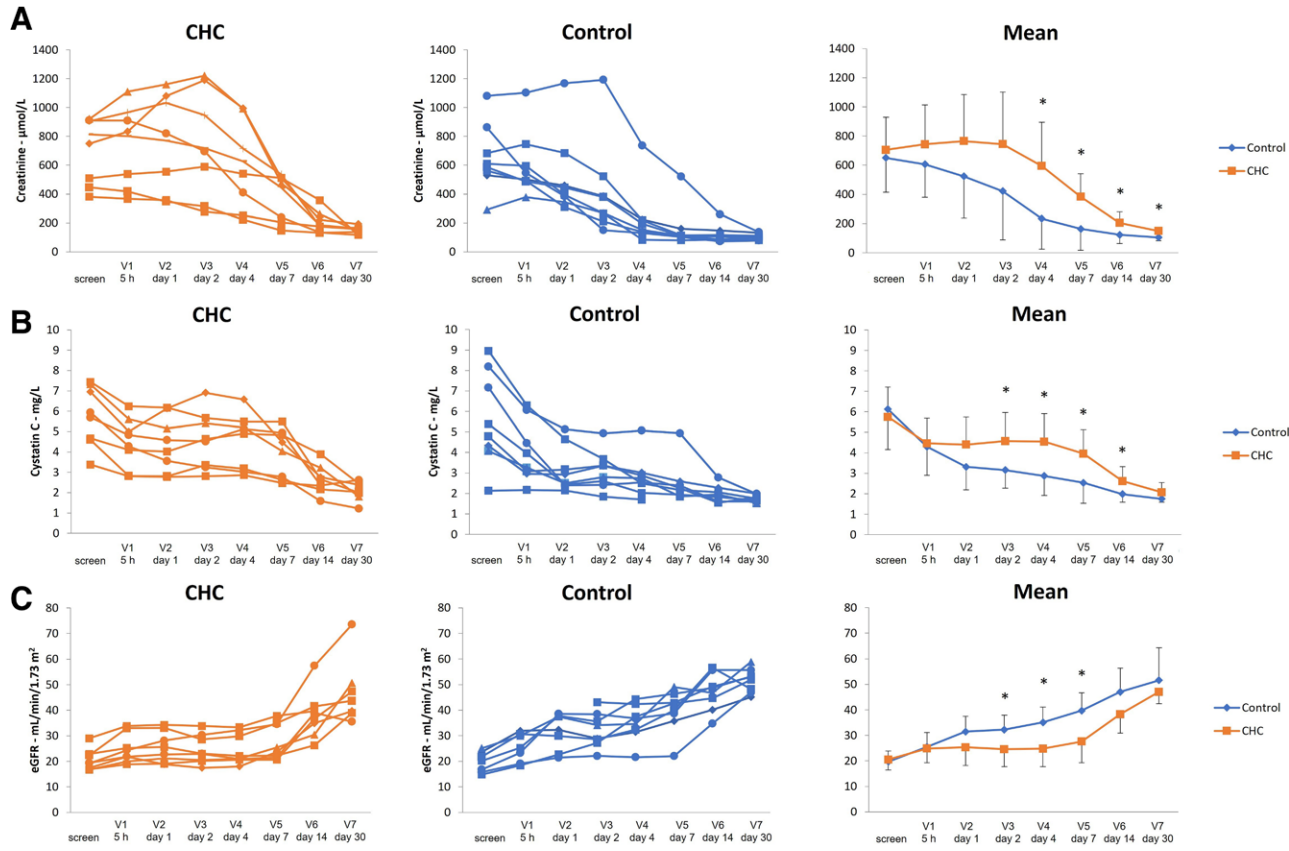

FIGURE 1. Levels of (A) serum creatinine, (B) serum cystatin C, and (C) eGFR (using the modification of diet in renal disease formula) in the enrolled patients. *$P \leq 0.05$ between groups in post hoc analyses. Visits: transplantation (visit 1), after 1 d ± 6 h (visit 2), 2 d ± 12 h (visit 3), 4 d ± 1 d (visit 4), 7 d ± 2 d (visit 5), 14 d ± 4 d (visit 6), and 30 d ± 4 d (visit 7). CHC, Corline Heparin Conjugate; eGFR, estimated glomerular filtration rate.

DISCUSSION

Results from this first-in-human trial indicate that CHC pretreatment of kidneys before transplantation showed no significant difference in the number and severity of AEs and SAEs compared with placebo; that is, the primary endpoint was reached. There was 1 SAE of postprocedural hemorrhage that led to reoperation. The volume of bleeding during the primary operation was higher in the CHC group than in the placebo group, with 1 patient in the CHC group bleeding 800 mL; however, volume values in both groups were judged to be clinically acceptable.

Renal function was very good in both groups, underlined by the fact that none of the patients experienced DGF. However, recovery of renal function, as measured by serum creatinine, serum cystatin C, and the MDRD formula over the first 7 d, seems to have been significantly slower, especially initially, in the CHC group, which conflicts with our preclinical data on efficacy.[15] Although delayed recovery of renal function may be a safety concern, it is difficult to interpret because the groups had different baseline characteristics. BMI and donor age were not equal between the treatment and placebo groups. Long-term follow-up of the patients will continue.

Interestingly, CHC uptake in these human kidneys from middle-aged donors occurred almost to the same extent as previously observed in kidneys from young pig donors.[15] Another important finding of our trial is the successful demonstration that drug delivery ex vivo is possible in clinical renal transplantation.

Regarding limitations, because dialysis was not required by any patients in the trial, safety issues that may manifest through dialysis sessions could not be detected. The sample size was relatively small, and kidney function was assessed over a short period; however, a larger planned phase II trial will provide further information on safety and efficacy.

To conclude, based on the analysis of the primary and secondary safety endpoints, pretreatment of kidneys with CHC before transplantation is considered safe and tolerable. Long-term follow-up of participants in the trial will continue for up to 5 y to provide additional safety and efficacy data. Clinical efficacy studies are now planned.

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