Effects of Dopamine Donor Pre-treatment on Graft Survival After Kidney Transplantation: A Randomized Trial

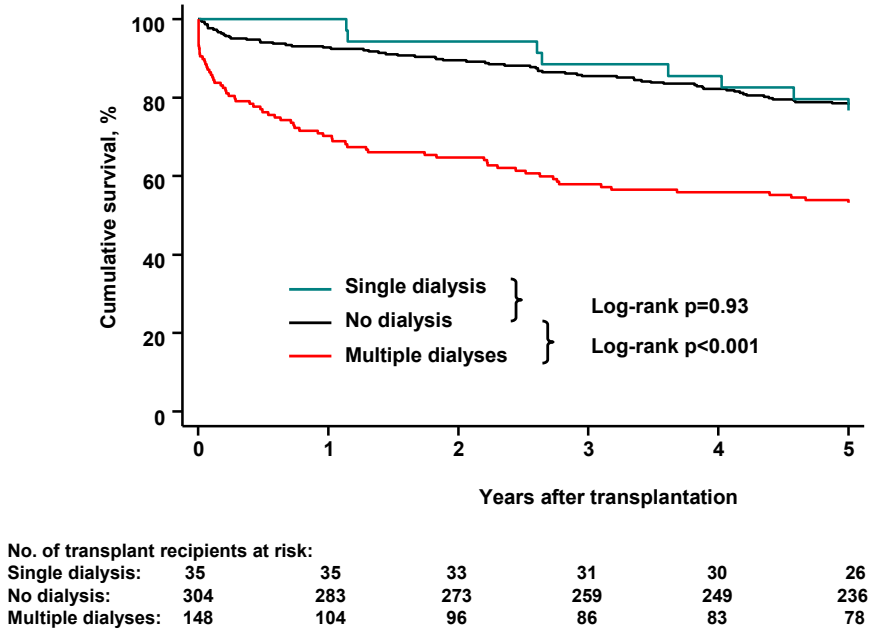
Supplemental Data

Definition of primary and secondary trial endpoints

The randomized dopamine trial was designed to test the hypothesis that a 4 μg/kg/min continuous dopamine infusion administered in the time window from ascertainment of brain death until cross clamping will reduce cold ischemic injury to the kidney graft. The primary trial endpoint was – different from the standard definition of DGF any dialysis treatment post-transplant – the use of more than one dialysis session during the first week after transplantation. Focusing on harm to the kidney graft, it was believed that multiple dialyses requirement was a more appropriate indirect parameter for deteriorated kidney graft function than a single post-transplant dialysis. A single dialysis session is more likely to be required because of the recipient's overall state of health and the physician's clinical judgement (7). This assessment is in retrospect proven true by supplemental figure 1 indicating that more than one dialysis session profoundly reduced the ultimate prognosis of the kidney graft whereas a single dialysis did not.

Using the standard definition of delayed graft function (DGF) failed to confirm the salutary effect of dopamine infusion time at the level of statistical significance (Supplemental Table 1). The most likely explanation is again that the conventional definition of DGF provides less selectivity to distinguish harm of the kidney graft from recipient related causes of dialysis use. It is obvious that treatment of the donor can neither influence nor improve the recipient's overall state of health at time of transplantation. On the other hand, there is little reason that recipient mandated indications of dialysis use post-transplant, such as hyperkalemia, post-operative volume overload, etc., will affect the long-term prognosis of the kidney graft. Secondary trial endpoints were incidence and severity of biopsy-proven acute rejection episodes within 30 days and patient and graft survival in the long-term (7).

Supplemental Figure 1.



Kaplan-Meier estimates of overall kidney graft survival until five years after transplantation according to dialysis requirement immediately after transplantation.

No dialysis requirement: 78.2%; 95%CI, 73.1 – 82.5%.

Single dialysis requirement: 76.7%; 95%CI, 58.7 – 87.6%.

Multiple dialyses requirement: 53.2%; 95%CI, 44.8 – 60.8%.

Supplemental Table 1. Multiple logistic regression of any dialysis requirement post-transplant.

Variable	OR	95% Confidence Interval	*P*-value
Dopamine infusion time, hours	0.98	0.93 – 1.03	0.42
Donor age, years	1.04	1.02 – 1.05	<0.001
Donor gender, female	1.28	0.83 – 1.98	0.27
Donor systolic blood pressure, mmHg	1.00	0.98 – 1.01	0.59
Donor diastolic blood pressure, mmHg	1.01	0.99 – 1.03	0.51
Donor urine production last hour, ml	1.00	0.998 – 1.002	0.87
Head trauma, yes	1.54	0.87 – 2.70	0.14
Cerebral stroke, yes	1.36	0.67 – 2.76	0.39
Cerebral ischemia/cerebral edema, yes	1.97	0.95 – 4.08	0.07
Time from admission on ICU to brain-death confirmation, days	1.01	0.97 – 1.06	0.63
Time from brain-death confirmation to organ procurement, hours	1.04	0.99 – 1.09	0.08
Multi-organ vs. kidney-only donor, yes	0.77	0.47 – 1.26	0.30
Cold ischemic time, hours	1.07	1.03 – 1.12	0.001
Recipient age, years	0.99	0.97 – 1.01	0.42
Recipient gender, female	0.78	0.49 – 1.22	0.28
Recipient weight, kg	1.01	0.99 – 1.03	0.15
Recipient diabetes, yes	1.61	0.83 – 3.09	0.15
Time spent on waiting list, years	1.02	0.95 – 1.11	0.54
Antigen mismatches A,B, and DR, No.	0.96	0.84 – 1.10	0.54
Panel reactive antibody >5%, yes	1.91	0.97 – 3.79	0.06
Repeat transplant, yes	1.18	0.63 – 2.20	0.60
Induction therapy, yes	1.34	0.88 – 2.02	0.17
Tacrolimus vs. Cyclosporine[§]	0.83	0.53 – 1.30	0.41

OR = odds ratio
[§] at time of transplantation

Ethical issues and informed consent for trial participation

Donor eligibility required the ascertainment of brain death in accordance with the guidelines of the scientific advisory council of the German Medical Association and consent to donation given in conformity with German transplantation legislation. During consultation with the relatives of the deceased to obtain informed consent for study inclusion, another physician not involved in the transplantation procedure was present and noted the contents and outcomes of the conversation. Provided that these conditions were met, the ethical commission agreed that obtaining separate hand-written consent for the study from the relatives was not necessary (7). Eligible recipients had to fulfill the usual criteria as a renal transplant candidate. We excluded recipients younger than 18 years. All transplant candidates who are placed on the waiting list sign their consent for the transmission of depersonalized medical data to the Eurotransplant database for scientific analyses. Before the prospective dopamine trial was initiated, we had undertaken a large registry-based cohort study that failed to demonstrate any negative effects of donor dopamine treatment but indicated a dose-dependent improvement on graft survival after kidney transplantation associated with catecholamine use, including dopamine (15). These findings were confirmed by another independent retrospective cohort study from our center (26). These retrospective studies also support that the prospective trial was carried out according to common practice in the management of a deceased heart beating donor, with the only difference that dopamine was administered under the surveillance of a controlled clinical trial. Moreover, current guidelines for the management of a brain-dead organ donor advocate the administration of dopamine up to a dosage of 10 μg/kg/min to maintain hemodynamic stability (3,4). Dopamine was administered at a dosage of 4 μg/kg/min, and both dopamine-treated donors and controls were carefully monitored to meet the target parameters of hemodynamic stability, so that irrespective of study assignment all donors were treated according to present guidelines.

Randomization was performed at a point when the graft recipient had not yet been selected. It was therefore not feasible to obtain informed consent from a recipient before the study medication was administered. This also precluded any timely decision by the recipient, with an intention to withdraw a particular donor from the trial if the recipient decided not to give informed consent. A patient awaiting an organ offer would have been excluded from receiving the kidney unless he or she decided to give informed consent for study participation. This would have produced an unacceptable ethical dilemma, given that the donor was treated with current standards of care.

Considering all these issues, the ethics committee decided to waive a requirement of written informed consent since no intervention in the recipients was mandated by the trial protocol. A standard information form for the recipients was sent with the kidneys, indicating the experimental design with regard to donor treatment and giving the recipients the opportunity to refuse participation in the data analysis without any penalty; all recipients agreed to participate (Schnuelle P, Yard BA. *JAMA* 303: 231-232, 2010).

Supplemental Table 2. Logistic regression of multiple dialyses requirement (>1 dialysis session) post-transplant excluding 42 kidneys not treated per protocol.

	Single-Variable Analysis			Multivariable Analysis		
Variable	**OR**	**95% Conf.-Interval**	***P*-value**	**OR**	**95% Conf.-Interval**	***P*-value**
Dopamine infusion time, hours	0.92	0.87 – 0.97	0.003	0.90	0.85 – 0.96	0.001
Donor characteristics						
Donor age, years	1.02	1.01 – 1.04	0.001	1.04	1.02 – 1.07	<0.001
Donor gender, female	1.29	0.86– 1.93	0.22	1.40	0.84 – 2.32	0.19
Donor systolic blood pressure, mmHg	1.00	0.99 – 1.01	0.98	0.99	0.98 – 1.01	0.54
Donor diastolic blood pressure, mmHg	1.01	0.99 – 1.03	0.34	1.01	0.98 – 1.03	0.60
Donor urine production last hour, ml	1.00	0.999 – 1.003	0.14	1.00	0.999 – 1.003	0.10
Cause of brain death						
Head trauma, yes	0.70	0.42 – 1.15	0.16	1.53	0.79 – 2.95	0.20
Cerebral stroke, yes	1.37	0.71 – 2.63	0.35	1.48	0.67 – 3.26	0.33
Cerebral ischemia/cerebral edema, yes	1.79	0.91 – 3.56	0.09	2.71	1.19 – 6.19	0.02
Time from admission on ICU to brain-death confirmation, days	1.00	0.96 – 1.04	0.89	1.00	0.95 – 1.05	0.99
Time from brain-death confirmation to organ procurement, hours	1.00	0.96 – 1.04	0.92	1.08	1.02 – 1.14	0.006
Multi-organ vs. kidney-only donor	0.72	0.45 – 1.15	0.17	0.87	0.50 – 1.51	0.61
Cold ischemic time, hours	1.08	1.04 – 1.12	<0.001	1.08	1.04 – 1.13	0.001
Recipient characteristics						
Recipient age, years	1.01	0.99 – 1.02	0.40	0.99	0.97 – 1.01	0.48
Recipient gender, female	0.74	0.49 – 1.13	0.17	1.10	0.66 – 1.84	0.72
Recipient weight, kg	1.02	1.01 – 1.04	0.001	1.02	1.01 – 1.04	0.02
Recipient diabetes, yes	0.82	0.46 – 1.47	0.50	1.28	0.61 – 2.69	0.51
Time spent on waiting list, years	1.02	0.95 – 1.10	0.61	1.03	0.94 – 1.12	0.54
Antigen mismatches A,B, and DR, No.	1.00	0.88 – 1.14	0.96	0.96	0.82 – 1.12	0.61
Panel reactive antibody >5%, yes	1.65	0.92 – 2.96	0.09	2.00	0.95 – 4.21	0.07
Previous transplant, yes	1.30	0.76 – 2.23	0.33	1.33	0.67 – 2.64	0.41
Immunosuppressive treatment[§]						
Induction therapy, yes	1.39	0.93 – 2.09	0.11	1.26	0.79 – 2.01	0.34
Tacrolimus vs. Cyclosporine	0.88	0.58 – 1.32	0.53	0.90	0.54 – 1.49	0.68

OR = odds ratio

[§] at time of transplantation

Supplemental Table 3. Cox regression of all-cause graft failure until five years after transplantation excluding 42 kidneys not treated per protocol.

	Single-Variable Analysis			Multivariable Analysis		
Variable	**HR**	**95% Conf.-Interval**	***P*-value**	**HR**	**95% Conf.-Interval**	***P*-value**
Dopamine infusion time, hours	0.95	0.91 – 1.00	0.04	0.94	0.90 – 0.99	0.02
Donor characteristics						
Donor age, years	1.03	1.02 – 1.05	<0.001	1.02	1.00 – 1.04	0.01
Donor gender, female	1.05	0.75 – 1.48	0.77	0.95	0.64 – 1.41	0.81
Donor systolic blood pressure, mmHg	1.01	1.00 – 1.02	0.04	1.00	0.99 – 1.02	0.54
Donor diastolic blood pressure, mmHg	1.01	0.99 – 1.02	0.47	1.00	0.98 – 1.02	0.93
Donor urine production last hour, ml	1.00	0.998 – 1.001	0.58	1.00	0.998 – 1.001	0.82
Cause of brain death						
Head trauma, yes	0.71	0.46 – 1.11	0.13	0.97	0.57 – 1.63	0.90
Cerebral stroke, yes	1.40	0.83 – 2.35	0.25	0.78	0.42 – 1.47	0.45
Cerebral ischemia/cerebral edema, yes	0.47	0.21 – 1.07	0.07	0.47	0.19 – 1.13	0.09
Time from admission on ICU to brain-death confirmation, days	1.00	0.96 – 1.04	0.99	1.00	0.97 – 1.04	0.85
Time from brain-death confirmation to organ procurement, hours	0.98	0.94 – 1.02	0.26	1.02	0.97 – 1.06	0.53
Multi-organ vs. kidney-only donor	0.87	0.58 – 1.28	0.47	1.03	0.66 – 1.61	0.90
Cold ischemic time, hours	0.99	0.96 – 1.02	0.49	1.00	0.97 – 1.04	0.92
Recipient characteristics						
Recipient age, years	1.04	1.03 – 1.06	<0.001	1.03	1.01 – 1.05	0.01
Recipient gender, female	1.19	0.84 – 1.68	0.32	1.41	0.94 – 2.11	0.10
Recipient weight, kg	1.00	0.99 – 1.02	0.46	1.01	0.99 – 1.02	0.24
Recipient diabetes, yes	1.18	0.75 – 1.87	0.47	2.07	1.21 – 3.55	0.008
Time spent on waiting list, years	0.98	0.92 – 1.04	0.54	1.01	0.94 – 1.08	0.83
Antigen mismatches A,B, and DR, No.	1.13	1.02 – 1.26	0.02	1.04	0.92 – 1.18	0.51
Panel reactive antibody >5%, yes	1.33	0.82 – 2.16	0.25	1.23	0.70 – 2.15	0.48
Previous transplant, yes	1.34	0.87 – 2.06	0.18	1.99	1.19 – 3.33	0.009
Immunosuppressive treatment[§]						
Induction therapy, yes	1.06	0.75 – 1.49	0.74	0.88	0.61 – 1.27	0.50
Tacrolimus vs. Cyclosporine	0.79	0.56 – 1.11	0.18	0.80	0.54 – 1.20	0.29

HR = hazard ratio

[§] at time of transplantation

Supplemental Table 4. Multiple Cox regression of all-cause graft failure taking infusion time ≥7.1 hours as cut-off value and implementing kidney donor profile index (KDPI) as independent explanatory variable. Donor age and cause of brain death are omitted from the analysis, because they are constituent parts of the KDPI.

Variable	HR	95% Confidence Interval	*P*-value
Dopamine infusion time ≥7.1 hours	0.54	0.30 – 0.98	0.04
Kidney donor profile index (KDPI), %	1.01	1.004 – 1.021	0.005
Donor gender, female	0.99	0.69 – 1.43	0.96
Donor systolic blood pressure, mmHg	1.00	0.99 – 1.01	0.85
Donor diastolic blood pressure, mmHg	1.00	0.98 – 1.02	0.96
Donor urine production last hour, ml	1.00	0.998 – 1.001	0.84
Time from admission on ICU to brain-death confirmation, days	1.01	0.97 – 1.05	0.69
Time from brain-death confirmation to organ procurement, hours	1.01	0.97 – 1.06	0.60
Multi-organ vs. kidney-only donor, yes	1.04	0.68 – 1.58	0.86
Cold ischemic time, hours	1.00	0.97 – 1.03	0.95
Recipient age, years	1.03	1.01 – 1.05	0.001
Recipient gender, female	1.38	0.94 – 2.04	0.11
Recipient weight, kg	1.01	0.99 – 1.02	0.17
Recipient diabetes, yes	1.74	1.05 – 2.86	0.03
Time spent on waiting list, years	1.00	0.94 – 1.07	0.90
Antigen mismatches A,B, and DR, No.	1.03	0.91 – 1.16	0.65
Panel reactive antibody >5%, yes	1.28	0.73 – 2.23	0.39
Repeat transplant, yes	2.00	1.21 – 3.28	0.006
Induction therapy, yes	0.84	0.59 – 1.20	0.33
Tacrolimus vs. Cyclosporine§	0.80	0.54 – 1.17	0.25

HR = hazard ratio
§ at time of transplantation

Supplemental Table 5. Serum-creatinine in patients with functioning graft five years after transplantation according to trial group assignment.

	Dopamine n=165	**No dopamine n=179**	***P*-value**
Serum-creatinine, mg/dl			0.83
<1.5, No. (%)	65 (39.4)	76 (42.5)	
1.5 – 3.0, No. (%)	62 (37.6)	65 (36.3)	
>3.0, No. (%)	13 (7.9)	10 (5.6)	
Missing values, No. (%)	25 (15.1)	28 (15.6)	

Supplemental Table 6. Serum-creatinine in patients with functioning graft five years after transplantation according to infusion time ≥7.1 hours as cut-off value.

	Dopamine ≥7.1h n=62	**Dopamine <7.1h n=282**	***P*-value**
Serum-creatinine, mg/dl			0.71
<1.5, No. (%)	26 (41.9)	115 (40.8)	
1.5 – 3.0, No. (%)	25 (40.3)	102 (36.2)	
>3.0, No. (%)	2 (3.2)	21 (7.4)	
Missing values, No. (%)	9 (14.5)	44 (15.6)	