Effect of N-Acetylcysteine Pretreatment of Deceased Organ Donors on Renal Allograft Function: A Randomized Controlled Trial

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Background. Antioxidant donor pretreatment is one of the pharmacologic strategy proposed to prevent renal ischemia-reperfusion injuries and delayed graft function (DGF). The aim of the study was to investigate whether a donor pretreatment with N-acetylcysteine (NAC) reduces the incidence of DGF in adult human kidney transplant recipients. Methods. In this randomized, open-label, monocenter trial, 160 deceased heart-beating donors were allowed to perform 236 renal transplantations from September 2005 to December 2010. Donors were randomized to receive, in a single-blind controlled fashion, 600 mg of intravenous NAC 1 hr before and 2 hr after cerebral angiography performed to confirm brain death. Primary endpoint was DGF defined by the need for at least one dialysis session within the first week or a serum creatinine level greater than 200 μmol/L at day 7 after kidney transplantation. Results. The incidence of DGF was similar between donors pretreated with or without NAC (39/118: 33% vs. 30/118: 25.4%; P = 0.19). Requirement for at least one dialysis session was not different between the NAC and No NAC groups (17/118: 14.4% vs. 14/118: 11.8%, P = 0.56). The two groups had comparable serum creatinine levels, estimated glomerular filtration rates, and daily urine output at days 1, 7, 15, and 30 after kidney transplantation as well as at hospital discharge. No difference in recipient mortality nor in 1-year kidney graft survival was observed. Conclusion. Donor pretreatment with NAC does not improve delayed graft function after kidney transplantation.

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protective effect of NAC for preventing the development of CI-AKI. In a randomized controlled trial, Koc et al. found that a prophylactic high dose of NAC reduced the occurrence of CI-AKI after coronary procedure. The KDIGO group suggests to administer NAC with an intravenous isotonic crystalloid in patients at risk to prevent CI-AKI. The impact of a pretreatment with NAC on kidney graft function has been evaluated in two animal models of kidney transplantation. N-acetylcysteine did not improve serum creatinine (Scr) levels nor histologic damages 24 hr after transplantation as compared with normal saline infusion. Lin et al. have shown that Scr and blood urea nitrogen (BUN) were lower at day 3 after renal transplantation. None of these studies assessed the incidence of DGF.

Considering its experimental antioxidant properties and vasodilatory effects, NAC might reduce ischemia-reperfusion injuries of kidney grafts. Our goal was therefore to investigate the effectiveness of a donor pretreatment with NAC at reducing the occurrence of DGF after kidney transplantation.

RESULTS

Baseline Characteristics

Of 251 patients evaluated for eligibility, 217 underwent randomization. Twenty-four of the 106 donors assigned to NAC treatment and 33 of the 111 donors assigned to No NAC treatment were excluded for various reasons (see Figure 1). Thus, a total of 82 and 78 donors in the NAC and No NAC groups, respectively, underwent kidney harvesting. One kidney per donor was transplanted in the study center with a frequency of 56% in the NAC group and 48.7% in the No NAC group ($P = 0.350$). Finally, 118 recipients received a kidney graft in each group, completed the follow-up study period and were analyzed (Figure 1).

Baseline and demographic characteristics of donors were similar in the two groups, except for age. Patients were significantly younger in the NAC group ($P = 0.02$). The number of donors who met the current United Network for Organ Sharing definition for expanded-criteria donor (ECD) kidney was comparable in the NAC and No NAC groups (15/82 [18.3%] vs. 23/78 [29.4%; $P = 0.105$]). Both groups were comparable with respect to hemodynamic and oxygenation conditions and renal function (Table 1). Factors conditioning kidney function and preservation before transplantation (flushing perfusion, ischemia time) were comparable between the two groups. Demographic, clinical recipients’ characteristics, and immunosuppressive therapy were similar in both groups. Major risk factors of DGF related to the donor (number of ECD), to kidney transplants conditions (prolonged ischemia time >24 hr), and to recipients (number of second transplant) were comparable in both groups (Table 1).

Endpoints

The incidence of DGF was comparable between the NAC and No NAC groups (39/118 [33%, 95% confidence

![Figure 1](https://www.journal.com/figure1.png)
TABLE 1. Demographic and baseline characteristics of donors and recipients

| Characteristics                        | Donors |        |        |
|----------------------------------------|--------|--------|--------|
|                                        | No NAC | NAC    |
| Age, mean (SD), yr                    | 50.5 (13.3) | 44.6 (15.5) |
| Men, No (%)                            | 56 (76) | 51 (62) |
| BMI, mean (SD), kg/m²                  | 25.2 (4.2) | 24 (3.9) |
| SAPS 2, mean (SD)                      | 51.7 (11.1) | 49.9 (13.8) |
| Cause of brain death                   |        |        |
| Trauma, No (%)                         | 30 (38) | 40 (39) |
| Intracranial bleeding/stroke, no (%)   | 48 (62) | 42 (51) |
| Donor type                             |        |        |
| Standard-criteria donor, no (%)        | 55 (71) | 67 (82) |
| Expanded-criteria donor, no (%)        | 23 (29) | 15 (18) |
| Cerebral arteriography, no (%)         | 49 (63) | 50 (61) |
| Volume of iodinated contrast medium, mean (SD), mL | 109 (58) | 119 (67) |
| Mean blood pressure during last 24 hr, mean (SD), mm Hg | 87 (19) | 85 (19) |
| Concomitant treatment                  |        |        |
| Desmopressin, no (%)                   | 52 (67) | 62 (76) |
| Norepinephrine, no (%)                 | 73 (94) | 79 (95) |
| Serum Creatinine during last 24 h, mean (SD), μmol/L | 77.7 (29.5) | 71.9 (26.7) |
| Urine output during last 24 h, mean (SD), mL | 3371 (2151) | 3667 (1785) |
| Mean pH during last 24 hr, mean (SD)   | 7.38 (0.09) | 7.39 (0.07) |
| Mean PaO₂ during last 24 hr, mean (SD), mm Hg | 130.6 (46.9) | 125.3 (39.5) |
| Measured creatinine clearance during last 24 hr, mean (SD), mL/min | 109.6 (58.4) | 113.9 (59) |
| Kidney transplants                     | n = 118 | n = 118 |
| Cold perfusion, no (%)                 | 99 (84) | 100 (85) |
| UW (Viaspan)                           | 19 (16) | 15 (15) |
| Cold ischemia time, mean (SD), hr²     | 15.5 (6.1) | 15.3 (4.9) |
| Prolonged ischemia time >24 hr, no (%) | 8 (6.8)  | 5 (4.2)  |
| Warm ischemia period, mean (SD), min²  | 38 (17) | 38 (14) |
| Anatomic graft risk factors, no (%)    | 24 (20.3) | 17 (14.4) |
| Recipients                             | n = 118 | n = 118 |
| Intraoperative mean systolic blood pressure, mean (SD), mm Hg | 118 (18) | 118 (13) |
| Intraoperative mean diastolic blood pressure, mean (SD), mm Hg | 62 (12)  | 61 (9)  |
| Intraoperative volume infusion, mean (SD), mL | 1780 (723) | 1690 (661) |
| Crystalloids                           | 491 (697) | 333 (329) |
| Age, mean (SD), yr                     | 50.4 (11.9) | 46.2 (13.8) |
| Men, no (%)                            | 73 (62) | 70 (59) |
| BMI, mean (SD), kg/m²                  | 23.6 (3.9) | 24.9 (4.6) |
| Second transplant, no (%)              | 12 (10.1) | 9 (7.6) |

Characteristics

| Characteristics                      | No NAC | NAC    |
|--------------------------------------|--------|--------|
| Kidney transplants issued from       |        |        |
| expanded-criteria donors, no (%)    | 31 (26.2) | 25 (21.2) |
| Immunosuppressive therapy, no (%)    |        |        |
| Ciclosporine                         | 20 (17) | 15 (13) |
| Tacrolimus                           | 100 (84) | 99 (84) |
| Mycophenolate                        | 112 (95) | 114 (87) |
| Corticosteroids                      | 114 (97) | 114 (87) |
| Recipient risk factors, no (%)       |        |        |
|                                     | 83 (70.3) | 91 (77.1) |

*Analysis performed using non-paired Student’s t-test for continuous variables and chi-squared test for categorical variables.

PB. 0.02 for comparison of No NAC and NAC group.

Data on warm ischemia period were not documented in 20 and 13 recipients of the NAC and the No NAC groups, respectively.

Graft risk factors for delayed graft function included arteriosclerotic renal vessels, abnormalities of renal vessels (atheroma, dissection, long arteriole) or kidney (cyst) or ureter (long, duplicated).

Recipient risk factors for delayed graft function included smoking, arterial hypertension, hyperlipidemia, obesity, lupus anticoagulant antibodies.

Data are expressed as mean (SD) for continuous variables, or frequency (%) for categorical variables. NAC, N-acetylcysteine; BMI, body mass index; SAPS, simplified acute physiology score; UW, University of Wisconsin; SD, standard deviation.

interval [95% CI] 24%–42% vs. 30/118 [25.4%, 95% CI 17%–34%]; P = 0.19 (Table 2). Dialysis during the first 7 days after transplantation was required in the same proportion of recipients of the two groups [17/118 [14.4%, 95% CI 8%–21%] vs. 14/118 [11.8%, 95% CI 6%–18%]; P = 0.56, respectively, in the NAC and No NAC groups (Table 2). We did not observe any adverse effect related to NAC administration.

At 1-day posttransplantation, Scr level, estimated glomerular filtration rate (eGFR), and daily urine production did not differ between the two groups. Serum creatinine level decreased comparably in both groups (P = 0.65) and within the first week after transplantation (P < 0.0001). The post hoc analysis showed that these variables did not change from day 7 to day 30 in both groups (Figure 2A). Both groups showed a comparable increased eGFR (P = 0.82) from day 1 to day 7 (P = 0.0001) and remained stable within the first month posttransplantation (Figure 2B). Daily urine production was unchanged at days 1, 7, 14 and 30 after renal transplantation (P = 0.17) and similar in the two groups (P = 0.82) (Figure 3).

There was no significant between-group difference in outpatient daily urine production, BUN, Scr level, and eGFR (Table 2). The proportion of kidney graft losses at 1 year after transplantation was comparable in the NAC and No NAC groups (9 [7.6%] vs. 11 [9.3%]; P = 0.57). The in-hospital length of stay of recipients was also comparable in the two groups. All recipients, but one, were surviving 1 year after transplantation. Kidney graft nephrectomy was performed within the first year in seven (5.9%) and eight (6.8%) patients, respectively, in the No NAC group and the NAC group.

DISCUSSION

The current study shows that a donor pretreatment with NAC failed to reduce the incidence and duration of DGF as compared with a control group. This result was associated with the absence of improvement in short-term renal graft function assessed by SCr, eGFR, and daily urine output.
within the first month after transplantation, and in 1 year recipients and graft function survival. Early renal graft dysfunction has several deleterious consequences. It has been demonstrated to be an independent risk factor for short-term acute transplant rejection and long-term chronic allograft dysfunction.4,15,16 Delayed graft function is also associated with an increased morbimortality in recipients. Most of those risk factors are related to donors’ and recipients’ conditions and management, and to organs’ preservation conditions.10 Consequently, major therapeutic goals aim to optimize tissue organ quality by maintaining renal oxygenation and perfusion, by shortening the ischemia period, by improving the quality of preservation solutions, and by preventing transplant immune rejection.

Recently, new pharmacologic strategies were proposed to prevent renal ischemia-reperfusion injuries and DGF.4,41 Subsequently, vasodilating agents, anti-inflammatory drugs, antioxidant agents, and modified small interfering RNA have been reported to improve organ dysfunction after ischemia-reperfusion in various experimental models. However, scarce clinical data remain conflicting.21,23-25 High doses of erythropoietin did not reduce the incidence of DGF in high-risk patients.25,26 Steroids pretreatment of organ donors was not able to reduce the occurrence of DGF despite a significant

| Primary endpoint                                      | No NAC (n = 118) | NAC (n = 118) | P<sup>c</sup> |
|-------------------------------------------------------|------------------|---------------|--------------|
| Delayed graft function, no (%)<sup>a</sup>            | 30 (25.4)        | 39 (33)       | 0.19         |
| Dialysis during first week posttransplant, no (%)<sup>a</sup> | 14 (11.8)        | 17 (14.4)     | 0.56         |
| Single session                                       | 9 (7.6)          | 4 (3.4)       |              |
| Multiple session                                     | 5 (4.2)          | 13 (11)       |              |
| No dialysis                                          | 104 (88.2)       | 101 (85.6)    |              |
| Serum creatinine >200 μmol/L                         | 16 (13.6)        | 22 (18.6)     | 0.45         |
| Secondary endpoints                                   |                  |               |              |
| Recipient in-hospital length of stay, mean (SD)<sup>b</sup> | 21.7 (8.4)       | 22.3 (10.3)   | 0.61         |
| Out-of-hospital urine output, mean (SD), mL<sup>b</sup> | 2,174 (338)      | 1977 (796)    | 0.27         |
| Out-of-hospital BUN<sup>b</sup>                       | 11.3 (6.3)       | 13 (16.9)     | 0.40         |
| Out-of-hospital serum creatinine, mean (SD), μmol/L<sup>b</sup> | 155 (122)        | 145 (73)      | 0.49         |
| Out-of hospital eGFR, mean (SD), mL/min<sup>b</sup>    | 52.9 (19.8)      | 52.9 (21.8)   | 0.99         |
| Graft loss at 12 mo, no (%)                           | 11 (9.3)         | 9 (7.6)       | 0.57         |

<sup>a</sup>Analysis performed using chi-square test.
<sup>b</sup>Analysis performed using non-paired Student t test.
<sup>c</sup>P for comparison of No NAC and NAC group.

Data are expressed as mean (SD) for continuous variables, or frequency (%) for categorical variables.

BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate using the Modification of the Diet in Renal disease (MDRD) formula.45

FIGURE 2. Time course of serum creatinine (A), eGFR (B) in the first month after renal transplantation assessed at days 1, 7, 14, and 30. Data markers represent the mean and the error bars, SD. Numbers of values at days 7, 14, and 30 were smaller than the number of recipients because of missing data and of patients discharged from hospital. A. The two-way analysis for repeated measurements showed that the factor time was significant (P < 0.0001), whereas both the factor group and the interaction between group and time were not significant (respectively, P = 0.653 and P = 0.472). *P < 0.0001 day 1 vs. days 7, 14, and 30 in both groups (post hoc analysis F Scheffe test). B, eGFR was calculated using the MDRD formula. The two-way analysis for repeated measurements showed that the factor time was significant (P < 0.0001), whereas both the factor group and the interaction between group and time were not significant (respectively P = 0.826 and P = 0.531). MDRD, Modification of the Diet in Renal Disease; eGFR, estimated glomerular filtration rate; SD, standard deviation.
suppression of inflammation and immune response in kidney grafts.\textsuperscript{24} Low-dopamine deceased heart-beating donor pretreatment was found to decrease the need for dialysis after kidney transplantation in a randomized controlled study.\textsuperscript{23} The administration of low-dose dopamine in living donors was also reported to improve the early renal graft function assessed by urine output during the first hours after transplantation, while Scr and BUN did not differ.\textsuperscript{27}

Among antioxidant drugs, NAC is safe and inexpensive. Moreover, it is commonly administered as a mucolytic agent and to treat acetaminophen poisoning. Experimental studies have shown that NAC improves ischemia-reperfusion injuries in various organs, such as the liver\textsuperscript{42} and the bowel.\textsuperscript{43} The impact of NAC has been widely evaluated during various renal ischemia-reperfusion conditions including CI-AKI and renal transplantation.\textsuperscript{7,22,28,29,36} The improvement of kidney injuries seems to result from several mechanisms associating decreased oxidative stress, nitric oxide-inhibiting effect leading to vasodilation, and preventive decrease in cytokine production and in apoptotic cell death.\textsuperscript{8,22,30,32,36,44}

To our knowledge, only two animal studies evaluated the impact of a pretreatment with NAC on renal graft function and reported conflicting results.\textsuperscript{22,46} Fuller et al.\textsuperscript{22} have found that histologic damages and Scr 24 hr after transplantation were comparable in rats pretreated with NAC as compared with those pretreated with mannitol or normal saline. However, NAC pretreated rats showed a better renal metabolism. Lin et al.\textsuperscript{22} have shown that pretreated dogs with two antioxidant molecules improved urine output and peak Scr posttransplantation. These effects were associated with a lower tumor necrosis factor-\(\alpha\), higher inducible nitric oxide synthase concentrations, and a decreased apoptosis. To date, our clinical study is the first to test whether a NAC donor’s pretreatment was able to improve renal dysfunction after transplantation. Our data failed to confirm this hypothesis, showing that this strategy did not reduce the incidence of DGF in our population of donors and recipients. Our results cannot be related to differences in major risk factors for DGF between groups which are completely comparable (same number of ECD, second kidney transplantation, and prolonged cold ischemia time). These conflicting results could be explained by methodological heterogeneities including large variability in doses, timing and route for NAC administration, cold ischemia period, and parameters for kidney graft function assessment. As reported previously, an artefactual effect of NAC on Scr level could have interfered with our results.\textsuperscript{23} However, such a confounding effect seems unlikely because we used a single small dose of NAC.\textsuperscript{24} Moreover, NAC administration to the donor cannot affect muscular creatinine production in recipients.

There are several limitations with this study. First, this is a single-blinded randomized monocenter trial. However, because of binding of intensivists, surgeons, and nephrologists in charge of the donors and the recipients, blinding of data management and analysis, it seems unlikely that the study design should induce any bias. Moreover, we choose to evaluate DGF as a primary endpoint because of its most consensual definition and assessment. Consequently, the requirement for dialysis within 7 days after transplantation would be unlikely to be influenced by any pretreatment ever known. Finally, we did not find any differences between groups in other biologic parameters of kidney graft function (Scr, daily urine production, and eGFR) at days 1, 7, 15, and 30 after transplantation and in 1-year kidney graft survival. Second, we did not analyze systematically graft biopsies that would allow us to identify acute transplant rejection and histologic injuries. Also, we did not measure accurately the renal blood flow nor biologic surrogate markers of oxidative stress to detect any hemodynamic or antioxidant effect of NAC. Thus, we cannot exclude any intracranial vasodilating or antioxidant effect of NAC in our population. Third, we did not focus on recipients receiving graft from expanded-criteria donors associated with prolonged ischemia time.\textsuperscript{4,45} Consequently, we cannot extrapolate our data for this subgroup of high-risk kidney grafts. Fourth, we choose to administer the most usual and empirically suggested dose that is based on the preventive action of NAC for CI-AKI.\textsuperscript{11} However, the optimal dose of NAC to prevent kidney transplant dysfunction is still unknown.\textsuperscript{46} The putative benefit of a higher dose or a longer period of NAC administration remains to be evaluated.

In conclusion, this study shows that NAC pretreatment of deceased heart-beating organ donors neither reduce the incidence of renal DGF nor improve daily urine production, Scr, and eGFR within the first month after transplantation.

**MATERIALS AND METHODS**

**Study Design and Patients**

This prospective, randomized, controlled open-label, monocenter study was conducted between September 2005 and December 2010 at the university hospital of Nice (with a final follow-up on December 2011). The investigators, the allograft recipients, and the physicians, who provided cares and renal function assessment, were blinded regarding donor’s pretreatment. The protocol was approved by the local institutional ethics committee (05-053 CPP Sud Méditerranée V), and a signed informed consent was obtained from the relatives of the donor and from the recipient.
Patients older than 18 years with all clinical signs of brain death were considered as eligible heart-beating donors. Patients presenting a preexisting chronic renal insufficiency (defined by a 24-hr measured creatinine clearance ≤ 30 mL/min) were not eligible. The diagnosis of brain death was legally declared after cerebral arteriography or computed tomography angiography. Exclusion criteria were consent refusals by the next-of-kin, medical contraindications for organ procurement, a presumed refusal organ donation, kidney graft stemming from another center, and medical complications before or during procurement leading to stop the procedure. A signed information was obtained from the donor’s relatives during the interview aiming to ask the presumed donor’s consent. Both the intensivist in charge of the patient and the local transplant coordinator were involved in this conversation which could be held before or after angiography. Thus, donors were excluded before or after randomization (i.e., angiography), in case of the absence of organ removal related to consent refusal, medical contraindications, or cardiac arrest.

**Treatment and Randomization**

One hour before the angiography diagnosis, brain-dead donors were randomly assigned in a 1:1 ratio using a computerized random-number generator list to receive or not receive NAC. The randomization code was not revealed to investigators, physicians who cared for renal transplantation and graft function. N-acetylcysteine (Flumucil; Zambon France, France) was administered as an intravenous bolus of 600 mg 1 hr before and 2 hr after cerebral or computed tomography scan angiography.

The French Biomedicine Agency was responsible for the allocation of kidneys to recipients. Renal distribution was not changed, giving priority to national emergent indications of transplantation and considering waiting time, cold ischemia time, usual compatibility criteria (human leukocyte antigen mismatch). Before being nominated on the waiting list, the transplant candidates had to fulfill and accept the usual conditions and rules of transplantation that were necessary for a definitive validation by the Biomedicine Agency. Candidates had also to sign an informed consent which stipulates clearly that they cannot know the identity of the donor nor choose their organ. They were also informed of the possibility to receive a kidney procured by a donor who was possibly participating in a clinical trial. Therefore, all recipients older than 18 years and transplanted at the study site were eligible. On the day of kidney transplantation, they were specifically informed of this study and were excluded in case of written consent refusal, but they were not allowed to refuse renal transplantation.

**Endpoints and Data Collection**

The primary endpoint was the incidence of DGF defined by the need for at least one dialysis session within the first week after kidney transplantation and a SCR level greater than 200 μmol/L at day 7 after transplantation.

Secondary endpoints included the evolution of renal graft function within 30 days after transplantation assessed by SCR, daily urine output, and eGFR at days 1, 7, 14 and 30 after transplantation. Estimated GFR was calculated according to the Modified Diet in Renal Disease formula. Other secondary endpoints were the in-hospital length of stay and mortality of recipients, the 1-year renal graft survival, and incidence of detransplantation. Investigators collected the donors and recipients baseline demographic characteristics, kidney transplant characteristics, and follow-up data on the recipients. Most significant risk factors associated with DGF were collected: 1) the number of ECDs defined by the United Network for Organ Sharing criteria; (2) the number of prolonged cold ischemia time defined by a delay >24 hr; (3) and the number of recipients receiving a second renal transplantation.

**Procedures**

The study protocol did not modify the global procedures. Management of heart-beating donors was consistent with the French guidelines aiming to maintain an appropriate organ perfusion and oxygenation (mean arterial pressure ≥65 mm Hg, PaO2 ≥80 mm Hg, central venous pressure 8–14 cmH2O, hemoglobin >7 g/dL, hourly diuresis ≥0.5 mL/kg/min). Organs were perfused in a cold preservation solution until transplantation. Management of recipients was performed as usual by nephrologists. The protocol of immunosuppressive therapy was left to the discretion of the nephrologist and included an induction therapy with a biologic agent (interleukin-2-receptor antagonist or a lymphocyte-depleting agent for kidney transplant recipients at high immunologic risk). Tacrolimus (Prograf; Astellas Pharma, France), aiming a target blood concentration between 8 and 15 ng/mL, was the first-line calcineurin-inhibitor used. Tacrolimus or cyclosporine (Sandimmun; Novartis Pharma, France) (target blood concentration from 150 to 250 ng/mL) was started at the time of transplantation. The antiproliferative medication consisted in the administration of 2 g intravenous daily mycophenolate mofetil (Cellcept, Roche, France) or 1.44 g orally daily enteric-coated mycophenolate sodium (Myfortic, Novartis Pharma). High dose of methylprednisolone (Solumedrol, Pfizer, France) (10 mg) was administered before transplantation followed by decreasing doses in the perioperative and the early posttransplant periods.

**Statistical Analysis**

Based on the French Biomedicine Agency data, we assumed that approximately 30% of kidney grafts would experience a DGF. Therefore, the inclusion of enough donors for 118 kidney graft recipients was required in each group to detect a 50% reduction in the proportion of DGF with a statistical power of 80% and a two-sided significance level of 0.05. Because of the rules of renal distribution, one or two kidneys from one donor could be available for transplantation at the study site. Thus, we presumed that donor inclusion would stop when each group of recipients reached 118. Because a mean of 50% kidney transplantations are realized in our study center, we calculated that time to complete our study will be 5 years.

Only organ donors who were successful in kidney transplantation in our study center were analyzed as well as all recipients receiving a kidney graft from donors of our study center. Analysis was conducted using a modified intention-to-treat way, with all the donors and recipients who met the inclusion criteria and completed the study. Descriptive statistics included frequencies (percentage and the 95% CI) for qualitative variables and mean (error standard) for continuous data. Comparison between groups was performed using the chi-square test and an unpaired Student t test when
appropriate (StatView 5.0, SAS Institute, Cary, NC). A two-way analysis of variance for repeated measurements was used to evaluate the interaction between time and group, followed by Scheffe F tests (intragroup and intergroup comparison) as post hoc analysis. A P value less than 0.05 was considered statistically significant.

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