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Effect of 1–28α-h atrial natriuretic peptide on acute renal failure in cadaveric renal transplantation

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Abstract: The efficacy and safety of (1–28) α-human ANP in preventing acute tubular necrosis (ATN) in cadaveric renal transplantation was tested by comparing ANP infusion with a maximal hydration (MH) regimen which we previously reported as effective in lowering the incidence of ATN (1, 2). Since the production of endogenous ANP increases with volume overloading (3), we hypothesized that increased endogenous ANP production may contribute to the beneficial effects of MH in renal transplant recipients. We thus conducted an open randomized study comparing the effect on early renal allograft function of MH (control group) versus moderate hydration plus ANP infusion (ANP group). Forty patients were blindly paired in two groups of 20 according to the duration of cold ischemia time (mean±2 h). The demographic characteristics of donors and recipients were similar. Using a Swan-Ganz catheter, hemodynamic parameters were monitored for 4 h after transplantation. The group receiving ANP and moderate hydration was perfused to a mean pulmonary arterial pressure (PAP) of ≤20 mmHg. The PAP in patients receiving MH was driven to ≥25 mmHg. In the ANP group, a bolus of 100 μg of ANP was infused into the graft's renal artery at the time of unclamping, followed by 24 h of continuous intravenous infusion at 0.03 μg/kg/min. Thereafter, the patients received ANP at a rate of 0.01 μg/kg/min until the serum creatinine reached <2 mg/dl. As a consequence of the hydration regimen, the PAP at unclamping was lower in the ANP group than in the control group; 20±3 and 26±4 mmHg, respectively ($p<0.05$). The ANP plasma levels were significantly higher during the first 3 d in the ANP group ($p<0.001$). The median recovery rate of renal function was similar in both groups. No patients in the ANP group experienced ATN while 4 patients (20%) in the control group did ($p=0.125$). The need for hemodialysis was markedly reduced in the ANP group compared to the control group (1 ANP-treated patient required dialysis once whereas 5 patients from the control group underwent dialysis a total of 26 times; $p=0.068$). ANP administration was well-tolerated and no hypotensive episodes were reported. This preliminary study suggests that ANP infusion is at least as effective as maximal hydration in preventing ATN and represents an efficient alternative for transplantation centers which do not use maximal hydration as a standard regimen in managing kidney allograft recipients.

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Introduction

Major progress in organ preservation and immunosuppression has recently been made, but primary non-function of cadaveric renal allografts remains a critical problem in cadaveric renal transplantation. This complication must be seriously considered since the scarcity of organs today fa-

vors the use of non-heart-beating donors, which significantly increases the incidence of ATN (4–7). Post-transplant ATN compromises the prognosis of kidney allografts in several ways, including rendering differential diagnosis between early technical failure, acute rejection and cyclosporin A (CyA) nephrotoxicity difficult. ATN also introduces dialysis-associated morbidity and impairs drug monitoring. But more importantly, according to most studies, ATN significantly reduces the long-term survival of kidney allografts (8, 9).

Measures to prevent post-transplant ATN include appropriate fluid management of the donor, reduction of the cold and warm ischemia time, and use of optimal conservation solutions (10–13). Preoperative mannitol and furosemide infusions, reduction or postponement of nephrotoxic drugs such as CyA, and optimization of the volemic status of the recipient have been shown to significantly reduce the incidence of ATN (1, 2, 13).We previously demonstrated that maximal hydration of renal transplant recipients under controlled hemodynamic monitoring by a Swan-Ganz catheter significantly reduced the incidence of ATN from 36% to 18% (1, 2). However, this technique is applied in only a few centers because it requires the use of a Swan-Ganz catheter, specially trained staff, and the technique is time- and cost-consuming. Maximal hyperhydration also carries the risk of overfilling (pulmonary edema) and there are infective risks associated with catheterization (14).

αh-ANP, a 28-amino-acid peptide which is secreted by the atrial appendages when distended by volemic overload, significantly increases natriuresis. One of the mechanisms by which ANP is natriuretic involves the increase of the glomerular filtration rate (GFR) through a vasodilation of the afferent arteriole and a vasoconstriction of the efferent arteriole. ANP also reduces the tubular reabsorption of water and sodium by a direct increase of pressure and flow in the vasa recta and by inhibiting the tubular effects of angiotensin II (3, 15–20).

We previously reported a significant correlation between ANP plasma levels and the maximal hydration regimen (21). We hypothesized that the beneficial effect of overloading on post-transplant ATN might be related to an increase of endogenous production of ANP. Experimentally, ANP has been extensively described as beneficial against renal ischemic injuries. In fact, in animal models infusion of ANP increases the GFR and natriuresis after ischemic insults, counteracts the toxic effects of CyA and protects the kidney in part by favoring a lower thromboxane B2/prostacyclin ratio in case of ischemia (22–40).

We therefore designed a trial comparing the previously described hyperhydration regimen (1, 2) and moderate hydration concomitant with infusion of ANP during and after kidney transplantation. Our results show that ANP plus moderate hydration provides, at the least, comparable results to maximal hydration in terms of ATN incidence, and thus suggests a beneficial effect of ANP on early graft function.

Methods

Design of study and selection of patients

The study protocol was approved by the Ethics Committee of the Catholic University of Louvain Medical School (UCL; Louvain-en-Woluwe). Since our previous results clearly demonstrated a significant decrease in ATN incidence with our preoperative maximal hydration regimen (1, 2), it was considered unethical to withhold this monitoring in the control group. Thus, we decided to compare the maximal hydration protocol to one including moderate hydration plus ANP infusion. Forty adult patients who gave oral informed consents were included in the trial. The kidney, provided through the Eurotransplant Organization (ET, Leiden, Netherlands), had a cold ischemia time of ≤48 h. The value of the median PAP at the time of induction of anesthesia (≤20 mmHg) was the preliminary criterion for the patient to be included in this trial, since if it was >20 mmHg, cardiopulmonary conditions might make randomization to maximal hydration hazardous. If the patient fulfilled the first criterion, s/he was stratified according to whether a first or a second renal allograft was due to be performed and then blindly assigned by a randomizing computer program to either the control group or the ANP group according to the expected cold-ischemia time ±2 h of the grafted kidney.

Treatments

During anesthesia and for the first 4 postoperative h all patients were monitored for PAP and wedge capillary pressure (PWCP) by a Swan-Ganz catheter, and for central venous pressure (CVP) and arterial blood pressure (BP) by appropriate catheters. Starting 30 min before unclamping of the kidney graft, all patients received 2 ml/kg 20% mannitol (Baxter, Belgium) within 25 min, an infusion of dopamine (Dynatra®; Sintesa) at a rate of 2 μg/kg/min and a 1 ml/kg infusion of antilymphocyte globulins (ALG; Boehringer Ingelheim) or antihymocyte globulins (ATG; Fresenius) in case of previous intolerance to the latter. Just before unclamping, 500 mg furosemide (Lasix®; Hoechst) and 250 mg hydrocortisone sodium

succinate (Solu-Cortef®; Upjohn) were given i.v. They also received i.v. administration of 1.5 mg/kg azathioprine (Imuran®; Wellcome) and then 6 h after declamping 1 g/65 kg methylprednisolone sodium succinate (Solu-Medrol®; Upjohn). Thereafter patients were given azathioprine 1 mg/kg/d and prednisolone 25 mg/d p.o. On d 1, oral cyclosporine (Sandimmun®, Sandoz) was initiated at 3 mg/kg and the dosage was thereafter adjusted to obtain a trough plasma level between 60–100 ng/ml. After d 30 prednisolone dosage was tapered to 10 mg/d. ALG was again given on d 2 and 3 at 1 mg/kg, and thereafter a 0.5 ml/kg for another 7 to 10 d.

Maximal hydration (control) group

According to the standard practice of the Center (1,2), the mean PAP was maintained between 20 and 28 mmHg by infusing 0.9% NaCl and 5% glucose in a ratio 2:1, plus 1 liter of plasma proteins for 3 liters of electrolyte solution. Packed red blood cells and whole blood were administered according to the preoperative losses to obtain a hematocrit of ≥25% at the end of surgery. Fluid administration was restricted when the PAP approached or exceeded 28 mmHg. Mannitol and/or furosemide were then given prn to sustain diuresis or if diuresis lagged behind fluid administration by more than 1 litre. This procedure was continued until diuresis reached >200 ml/h, for a maximum of 4 h. Thereafter, infused volumes and fluid intakes were at least 2 l/d and 500 ml above diuresis output.

ANP group

Lyophilized synthetic (1–28) α-hANP was supplied by Bioproducts S.A. (UCB, Braine L'Alleud, Belgium). At unclamping, a bolus of 100 μg ANP was injected into the renal artery. Patients were hydrated to maintain a PAP in the vicinity of but not above 20 mmHg. An intravenous 24-h ANP infusion at the rate of 0.03 μg/kg/min was initiated at the onset of the anastomosis of the kidney. αh-ANP was diluted in NaCl 0.9% containing 1% human albumin and infused in a 50 cm^3 pulsed syringe within 24 h of unclamping. If, after 4 h, diuresis was less than 200 ml/h, or artrial hypertension developed, or the PAP exceeded 20 mmHg, mannitol and/or furosemide was administered prn. Beginning on d 2, ANP was infused at a rate of 0.01 to 0.03 μg/kg/min according to diuresis (the rate was increased when diuresis lagged behind the infusion rate, which was at least 2 l/d). ANP was given for a maximum of 8 d or until plasma creatinine was ≤2 mg/dl.

Patients surveillance and biological assessment

During the first 2 postoperative d, patients' vital functions and diuresis output were monitored hourly. The hematocrit, ionogram, plasmatic level of creatinine and ANP, as well as the urinary volume and urinary creatinine, were assessed at the induction of anesthesia, at the start of anastomosis, at the time of unclamping, every hour for 4 h after unclamping, and every 4 h during the first 24 h. Starting d 1, ANP plasma levels and trough plasma levels of CyA were measured every morning as well. Other plasmatic or urinary parameters were assessed daily for the first 2 postoperative wk: plasmatic aldosterone and renin, and urinary proteins such as retinol binding protein (RBP), β-*N*-acetyl-D-glucosaminidase (NAG), prostacyclin (PGI2) and cyclic guanosine monophosphate (cGMP).

Assessment of acute kidney dysfunction

Initial kidney dysfunction was diagnosed if during the first 2 postoperative d (in the absence of other recognized causes) the patient remained or became anuric or oliguric with a positive fluid balance >3 l and/or hyperkalemia >5.6 mEq/l. As previously described by Halloran et al. (8), ATN was diagnosed when kidney dysfunction persisted and the patient required hemodialysis more than once during the 1st wk after transplantation. All other impaired clinical courses were diagnosed as transient renal dysfunction.

Acute graft rejection was diagnosed if during the 1st postoperative wk the plasma creatinine increased, renal perfusion decreased by >30% at scintigraphy and there were clinical signs of decreased diuresis, edema and hypertension. If renal dysfunction appeared 7 d after transplantation, the diagnosis was confirmed histologically by ultrasound-guided fine needle renal biopsy. Pulsed doses of methylprednisolone associated with ATG or muromonab-CD3b (Orthoclone OKT3®; Ortho-Cilag) were administered and, if necessary, hemodialysis was initiated.

CyA nephrotoxicity was defined as increased plasma creatinine in the presence of CyA plasmatic levels ≥100 ng/ml and absence of concomitant signs of rejection or surgical complications. CyA dosage was then adjusted.

Statistical analysis

Nonparametric, paired, two-tailed tests were used. The comparison of quantitative variables was performed by Wilcoxon signed rank test; the p value was extracted from tables of exact distribution and

computed by normal approximation. The comparison of qualitative variables was performed by binomial test with exact p value. Inference was only undertaken when at least 10 paired values were available. No correction for multiple comparisons was applied. The results are expressed as mean±SD. A p value of <0.05 was considered statistically significant.

Results

Three patients randomized into the control group were included in the trial but were not paired with a patient in the ANP group before the 20 pairs were completed, and were thus excluded. One patient had a mean PAP>20 mmHg at the time of anesthesia induction and was therefore excluded as required by the protocol. One patient receiving a second kidney transplant was included in the ANP group but at the time of ALG infusion developed an anaphylactic reaction with shock and severe hypotension. This patient was excluded from the study since the hypovolemic shock subsequent to the ALG treatment may have been deleterious for the function of the renal allograft. The possibility of the involvement of ANP in the hypotensive shock is ruled out by the fact that successful ANP infusion was performed at a later time.

As shown in Table 1, the demographic characteristics of the recipients were similar in both groups. Similarly, as illustrated in Table 2, the characteristics of the donor and the kidney transplant were comparable. The cold ischemia time, which was the main criterion for pairing the patients, was similar in both groups: 26.3±6.6 h in the ANP groups vs. 26.4±6.8 h in the control group (16 to 43.5 h). The second warm ischemia time (time for anastomosis) was comparable in both groups (37±8 min in the ANP group and 34±6 min in the control group). Hemoglobin at declamping was 9.1±1.8 g/dl in the ANP group and 8.4±1.3 g/dl in the control group. As expected and shown in Table 3, patients in the control group had received more fluids than ANP-treated patients (2.7±0.7 l vs. 1.8±0.7 l, respectively) by the time of unclamping. The 1 litre of excess fluids was constituted by approximately equal volumes of cristalloids and blood. However, the total volume of fluid infused during the 24 h after unclamping was comparable in the ANP group (mean=9.7±3.4 l; range 2.7–18.0 l) and in the control group (mean=8.2±4.2 l; range 2.2–18.2 l). Similarly, the total urinary output during the 24 h after unclamping was similar in both groups: 8.4±4.4 l (range 0.9–20.3 l) in the ANP group and 8.1±6.0 l (range 0.1–23.5 l) in the control group.

Table 1. Characteristics of the recipients

	ANP group	Control group
Age (years, mean±SD)	36±8	38±8
Weight (kg, mean±SD)	64±11	61±8
Sex ratio (M/F)	16/4	12/8
Time in dialysis (months, mean±SD)	54±39	39±31
Time from last dialysis (days, mean±SD)	1.4±1.0	1.3±0.9
Panel reactive antibodies (%, mean±SD)	9±21	11±18
HLA mismatches:		
A (0, 1, 2)	9, 5, 6	7, 10, 3
B (0, 1, 2)	9, 9, 2	5, 15, 0
DR (0, 1, 2)	18, 2, 0	16, 3, 0*
Cause of renal failure:		
Glomerulonephritis	9	11
Pyelonephritis	3	1
Hypertension	0	2
Congenital	3	1
Polycystic	2	2
Vascular	1	1
Other	2	2

*One result missing.

Table 2. Characteristics of the donors and the transplanted kidneys

	ANP group	Control group
Age (years, mean±SD)	31±11	31±14
Sex (M/F)	12/8	12/8
Plasma creatinine (mg/dl, mean±SD)	1.03±0.29	1.07±0.30
Warm ischemia (min, mean±SD)	0.1±0.2	0.5±1.3
Cold ischemia (hours, mean±SD)	26.3±6.6	26.4±6.8
Cardiac arrest (n, duration)	1, 10 min	1, 10 min
Cause of death:		
Trauma	11	13
Cerebral hemorrhage	8	7
Brain tumor	1	0
Type of harvesting (kidney/multiple organs)	3/17	6/14
Preservation fluid (EC, UW, HTK)*	5, 14, 1	7, 12, 1
Volume preservation fluid (l, mean±SD)	3.70±3.98	3.03±0.95
Harvesting team (UCL/Others)	4/16	4/16

* EC (Euro-Collins), UW (University of Wisconsin), HTK (Histidine-Tryptophan-Ketoglutarate fluid of Bretschneider).

Table 3. Results

	ANP group (n=20)	Control group (n=20)
Systolic blood pressure (H0) (mmHg)	145±17	140±20
CVP (H0) (cm of water)	12±4	19±5*
PAP (H0) (mmHg)	20±3	26±4*
PCWP (H0) (mmHg)	13±4	17±3
Infused fluids (ml) (H0)	1769±669	2737±692
Urinary flow (ml/h) (H24)	200±165	148±147
ATN	0	4
Number of dialyses	1	26
Plasma renin activity (mg/ml/h) (Day 1 - >Day 10)	<0.2	<0.2
Plasma aldosterone (nM/l) (Day 3)	<0.01	0.56±0.65*

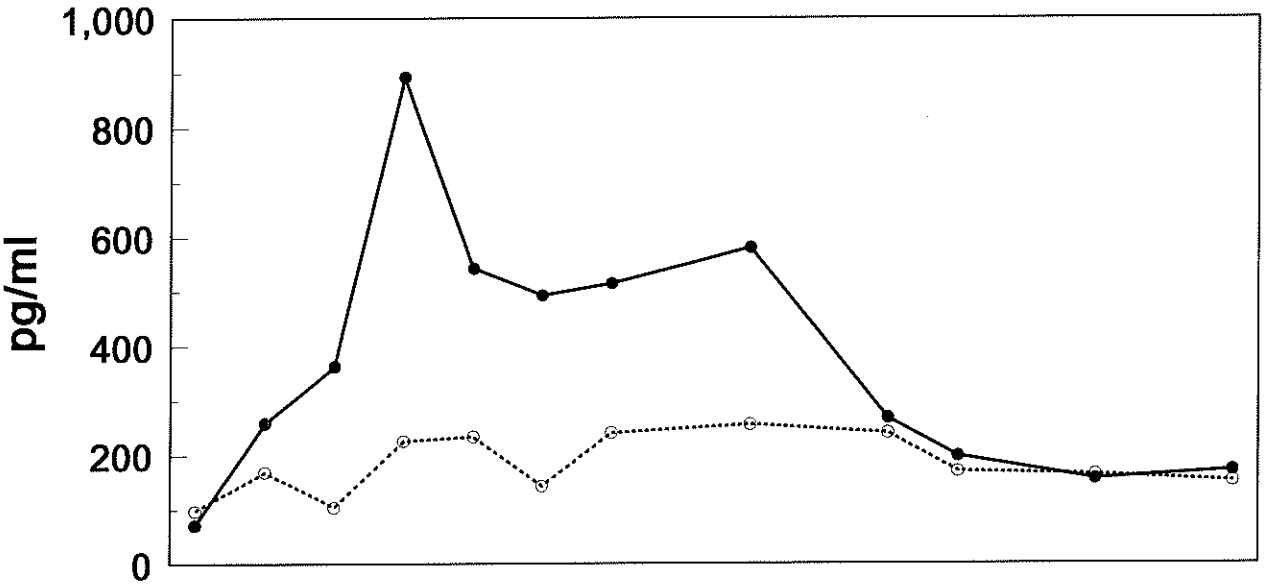
* $p<0.05$.

Upon unclamping, the systolic and diastolic blood pressures were similar, while the CVP, PCWP and PAP were significantly higher in the control group as a consequence of the maximal hydration regimen. As intended in the protocol, the PAP at the time of unclamping reached 20±3 mmHg in the ANP group and 26±4 mmHg in the control group ($p<0.05$). There were no hypotensive episodes recorded during ANP infusion in the 20 patients of the ANP group. There were no obvious differences between the two groups in the hemodynamic parameters after unclamping. After removal of the Swan-Ganz catheter, hydration was performed in both groups while monitoring blood pressure, CVP and urinary output. The CVP and blood pressure during the first postoperative 24 h were comparable in both groups; the CVP was constantly>6 cm of water (range 6–19) and the systolic blood pressure was constantly>140 mmHg (range 142–189).

Finally, from the time of unclamping until postoperative d 3, the dosage of plasmatic ANP was significantly higher in ANP-treated patients than in control patients, ($p<0.001$) (Fig. 1). The duration of the ANP treatment varied from 4 to 14 d. In 4 cases, treatment was discontinued before a plasma creatinine value of ≤2 mg/dl was reached.

1. Efficacy

Four patients in the control group (20%) developed ATN versus 0 patients in the ANP group ($p=0.125$). In the control group, in addition to the 4 cases of ATN (Fig. 2A), 2 patients experienced transient renal dysfunction, among whom 1 required a single dialysis on d 7 because of a positive fluid balance of 7 l. In comparison, 4 patients in the ANP group experienced transient renal dysfunction, which resolved promptly and spontaneously (the clinical course of 1 representative recipient is illustrated in Fig. 2B). Among them, 1 patient underwent hemodialysis once on d 2 because of transient anuria with a kalemia reaching 6.7 mEq/l, immediately following the first CyA administration (Fig. 2B). Overall, 16 patients in the ANP group and 14 patients in the control group recovered a good early graft function (the clinical course of 1 representative recipient is illustrated in Fig. 2C). The time to halving (t 1/2) of the preoperative plasma creatinine level was 31 h in the ANP group and 37 h in the control group. The mean plasma creatinine level of d 7 was 2.44±1.52 mg/dl (range 1.05 to 6.9 mg/dl) in the ANP group and 3.93±3.67 mg/dl (range 0.9 to 11.65 mg/dl) in the control group.



	induction	anastomosis	H0	H4	H20	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12
ANP pg/ml ●	71	259	363	893	543	493	516		581		268	198		156		172
Control pg/ml ⊖	97	169	104	226	234	143	241		256		241	170		164		152

Fig. 1. Course of mean ANP plasma levels (pg/ml) in ANP (●) and control group (O) (induction to postoperative day 12).

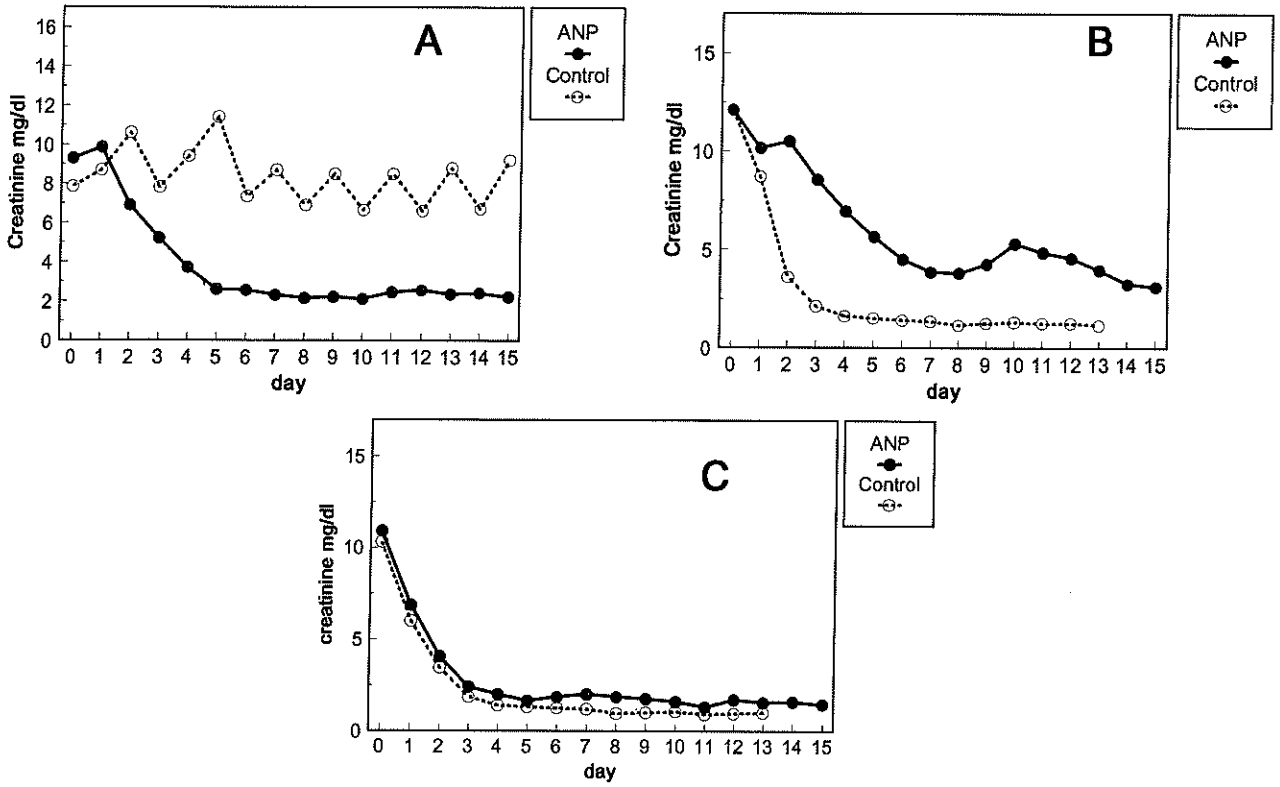


Fig. 2. Clinical course of renal function in representative cases of both groups. A: ATN in 1 control-patient and rapid renal function recovery in 1 ANP-patient. B: clinical course of transient renal dysfunction in 1 ANP-treated patient and normal clinical course in a control patient. C: 2 patients with a good early recovery of renal function.

As previously mentioned, 1 ANP-treated patient required dialysis once, whereas 5 patients in the control group underwent dialysis a total of 26 times (number of dialyses per patient=1, 3, 5, 7 and 10 respectively) ($p=0.068$). To sustain diuresis output or to correct for a lag of diuresis output behind fluid administration, patients in the control group were given mannitol and/or furosemide. The ANP group was given a transient increase in the rate of ANP infusion. ANP infusion was increased on d 2 in 2 patients. One of the 2 patients also received furosemide and mannitol. During the stay in the Transplant Unit, a total of 3480 mg of furosemide was administered to ANP-treated patients versus a total of 7600 mg to patients in the control group ($p=0.409$). Most administrations occurred during the first 4 d. Per patient, the total amounts of furosemide administered (median, extremes) were 120 mg (0–740) in the ANP group and 140 mg (0–1380) in the control group. Two times less ANP-treated patients (6 ANP vs. 12 control patients) required furosemide during the first 24 h after transplantation, i.e. for early kidney dysfunction.

The median of the plasmatic CyA levels remained below the quantification limit until d 4. Similar stabilized median levels (between 35 and 40 ng/ml) were attained from d 9 on. No significant differences were found within the two groups in the means of several biological assessments i.e. creatinine clearance, plasmatic and urinary ionogram, plasmatic renin, urinary NAG, RBP, PGI2 and cGMP. The aldosterone plasmatic level, however, was significantly higher in the control group ($p<0.05$).

Within the 1st postoperative month, 5 ANP-treated patients presented acute cellular rejection versus 9 patients in the control group ($p=0.289$). In addition, two surgical complications occurred; early leakage of the uretero-cystostomy in an ANP patient and necrosis of the ureter in a patient from the control group. These problems were resolved by remedial surgery. At 3, 6 and 12 months, the creatinine level was similar in both groups (ANP vs. control): 1.48 vs. 1.39; 1.56 vs. 1.56; 1.36 vs. 1.61 mg/dl, respectively. One patient in each group underwent a transplantectomy for chronic rejection at 12 and 14 months.

2. Safety

One ANP patient developed ascites associated with a perirenal hemorrhage of unknown origin. ANP was stopped on d 8 as a precautionary measure, as the plasma creatinine had reached 4.9

mg/dl without any apparent effect on the evolution of this complication. Worthy of note, however, is that biopsy showed acute rejection. No other unexpected events were reported. In particular, there were no reports of hypotension.

Discussion

This open randomized pilot study suggests that ANP infusion during and after kidney transplantation instead of maximal hydration during the transplant procedure decreases the incidence of ATN (0/20 in the ANP group vs. 4/20 in the control group ($p=0.125$)). Only 1 ANP-treated patient required dialysis once whereas 5 patients in the control group required dialysis a total of 26 times ($p=0.068$). Additionally, the need for diuretics was lower in ANP-treated patients than in patients from the control group. Although the differences between the two groups do not reach statistical significance, a trend in favor of ANP treatment is apparent. The absence of statistical significance in this study may be due to: (1) the small number of patients in each group; (2) paired design which requires stringent statistical analysis; and (3) comparing ANP infusion not to standard monitoring but to optimal intra-operative management (maximal hydration) which has previously been shown to lower significantly the incidence of ATN (1,2). Overall, we found 20 % ATN incidence in the control group, which is similar to the previously reported incidence (18%) using maximal hydration (1, 2). The absence of ATN in the ANP-treated group therefore suggests that ANP represents an improvement. In fact, assuming that both treatments would actually be equally effective, the probability that ANP infusion with moderate hydration being less effective than maximal hydration is only 0.063. The probability of the ANP treatment being a better treatment that maximal hydration therefore is 93.7%. Although preliminary, these results indicate that ANP infusion concomitant with moderate hydration can be considered to be at least as effective as maximal hydration in lowering ATN incidence. This treatment thus represents an alternative regimen for the management of renal transplant recipients in centers which do not use maximal hydration in preventing ATN.

Other clinical trials studying the effect of ANP in renal transplant recipients have reported negative or mitigated results. It is therefore necessary to review the other protocols in order to explain the difference in results. Even though other amino acid sequences or analogs were used in these studies reviewed, it is more important to carefully analyze the experimental conditions of these previously reported trials. For instance, in a pilot study conducted by Bozkurt et al., 6 oligoanuric or anuric patients were treated with ANP. Significant increased diuresis output was observed in only 2 patients (41). These patietns were infused with an intravenous bolus of αh-ANP (100 μg) 3 h after unclamping, followed by a 30 min infusion of 600 μg. The short duration of ANP infusion (the half-life of ANP does not exceed 2–3 min) and the fact that these patients suffered from previously established ATN, represents two major obstacles to any beneficial effects (42). Similarly, Smits et al. reported the absence of beneficial effects after ANP infusion in 16 renal transplant recipients when ANP was infused into the kidney artery for 46 min at a rate of 0.05 μg/kg/min, followed by i.v. administration for ±2 h (43). Although this study was well conducted, it was not randomized and it remains unexplained as to why, when a concomitant mannitol infusion was reintroduced in the protocol, these authors still had a 44% incidence of ATN, whereas they previously demonstrated that mannitol alone is capable of decreasing the rate of ATN to less than 20% (37). Two other double-blind randomized and paired studies also failed to demonstrate significant beneficial effects of ANP infusion on early renal function in transplant recipients (44, 45). In the first study, 1–28 αh-ANP was infused intravenously for 4 h after a previous intra-renal bolus of 50 μg. In the second study, an analog (atriopeptin III) was infused intravenously for 12 h. In addition to a longer period of ANP infusion, the patients in these studies received significant fluid loading since the CVP reached a mean of 6.3 cm of water (range 5–10), ruling out the possible implication of hypovolemic status as the cause of the unsuccessful results. Although these studies were also well conducted, they did not demonstrate significant beneficial effects with ANP in terms of ATN. In the first study, 3/10 ANP-trated patients developed ATN versus 4/10 in the control group. In the second study, 5/10 patients in the control group had ATN versus 3/10 in the ANP-treated group.

Although the results in our study are not statistically significant, the trend is in favor of the use of ANP infusion after renal transplant. Differences which may explain such favorable results in comparison to the previously reported studies are: even if hydration of the ANP-treated patients was not maximal, they received significant hydration since the CVP was 12 cm of water at the time of unclamping and pressure was significantly higher in patients in our study than in the studies discussed above; secondly, the time of infusion was longer since we maintained the ANP at a low dose until the creatinine reached 2mg/dl, which required on average 1 wk. As shown, several conditions must

be present for ANP to be effective in the prevention of posttransplantation ARF. Failure to meet these conditions may account for the inconclusiveness of the previously published studies. In summary, (1) An adequate dose and dose rate must be used since ANP has a very short half-life. However, low doses of ANP have been reported as natriuretic in patients in chronic renal failure and in transplanted patients receiving CyA (46, 47); (2) An adequate duration of ANP administration is important although, in all the successful animal experiments reported in the literature, the duration of infusion was usually short (25–35). One reason we think that the duration of ANP infusion is important is that, in renal transplant recipients, the addition of CyA, which has well known nephrotoxic side effects, might be advantageously counteracted by long-term ANP infusion (40); (3) Timing of initiation of ANP treatment appears to be crucial. When ATN lesions are established and all the tubules are swollen and obstructed by casts, the higher fraction filtration induced by ANP may be unable to reverse established ATN. However, this last explanation is not plausible since a recent study of Rahman et al. clearly demonstrated that ANP is able to decrease significantly the incidence and severity of ATN in patients suffering from established intrinsic acute renal failure (48); (4) Finally, in order for ANP to be efficient, a threshold blood volume and blood pressure may be required since this endogenous hormone has been described as effective physiologically only in the context of fluid overloading. In fact, ANP has been reported as a weak diuretic in dehydrated patients (49). Therefore these conditions must be fulfilled for ANP to be natriuretic.

In conclusion, this study shows that ANP is well-tolerated and allows use of a hydration regimen less vigorous than maximal hydration. Since the number of patients with ATN decreased and the total number of dialyses required was markedly reduced, combining ANP with a moderate hydration regimen appears to be at least as effective as maximal hydration. In fact, the probability that it would be less effective is minimal. With the exception of patients with high cardiovascular risk, hydration of future ANP cases could be performed under sole monitoring of the CVP, thus dispensing with the use of a Swan-Ganz catheter, which is known to involve vascular, infectious risks (14, 50) and high costs. Moreover, considering the more rapid recovery of renal function, another advantage of ANP administration is better identification and hence a more appropriate treatment of acute rejection episodes during the initial post-transplant period. Finally, since early recovery of adequate post-transplantation renal function appears to be a major prognostic factor for renal allograft survival, this study suggests that ANP could become a therapeutically and economically beneficial alternative regimen in the field of renal transplantation.

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