Mannitol and Renal Dysfunction After Endovascular Aortic Aneurysm Repair Procedures: A Randomized Trial

Konstantinos Kalimeris, MD, PhD,* Nikolaos Nikolakopoulos, MD,* Maria Riga, MD,* Kalliopi Christodoulaki, MD,* Konstantinos G. Moulakakis, MD, PhD,† Cleanthi Dima, MD, PhD,‡ Christos Papasideris, MD,† Tatiana Sidiropoulou, MD, PhD,* Georgia Kostopanagiotou, MD, PhD,* and Angeliki Pandazi, MD, PhD*

Objective: **Endovascular aortic aneurysm repair (EVAR) may result in deterioration of renal function. Mannitol has renovascular and antioxidant properties that could prove beneficial in this respect.**

Design: **A randomized prospective study.**

Setting: **Attikon University Hospital, single institution.**

Participants: **Eighty-six patients undergoing elective EVAR under regional anesthesia.**

Methods: **Patients received hydration alone (controls) or hydration plus mannitol (0.5 g/kg).**

Measurements and Main Results: **Creatinine, serum cystatin-C, urine neutrophil-gelatinase-associated lipocalin (NGAL), albuminuria and serum urea were measured 24 hours and 72 hours after the procedure (baseline NGAL was measured in 19 randomly selected patients). Serum creatinine also was measured at the followup of the patients. Serum creatinine and cystatin-C were lower in the mannitol group at 24 hours postoperatively (creatinine, mannitol [n = 43]; 1.07 ± 0.26 [CI95%: 0.99-1.15] *v* controls [n = 43]; 1.20 ± 0.30 [CI95%: 1.11-1.30]), but not at 72 hours (creatinine, mannitol [n = 43]; 1.13 ± 0.29 [CI95%: 1.04-1.22] *v* controls [n = 43]; 1.26 ± 0.41 [CI95% 1.15 – 1.38]). Urine NGAL increased substantially at 24 hours without differences between groups. At followup (controls: 13 ± 7 months; mannitol: 12 ± 7 months), there were no differences between creatinine or creatinine clearance (creatinine: controls [n = 28]; 1.15 ± 0.39 [CI95% 1.02-1.29] *v* mannitol [n = 23]; 1.05 ± 0.27 [CI95%: 0.95-1.17]). The overall changes of creatinine and creatinine clearance with time were significant in controls but not in the mannitol group. The classification according to the RIFLE criteria yielded 4 patients at risk for renal injury and 2 with renal injury in the control group and 6 patients at risk with no patients with injury in the mannitol group, but the difference of renal dysfunction between the 2 groups was not statistically significant.**

Conclusions: **Mannitol plus hydration during EVAR provides a small but significant benefit for renal function. Future preventive protocols aiming at greater restoration of renal function after EVAR could include mannitol as a useful component.**

KEY WORDS: ***endovascular aneurysm repair (EVAR), renal function, mannitol, acute kidney injury***

DESPITE THE AVOIDANCE of aortic cross-clamping, hemodynamic instability, and ischemia-reperfusion in endovascular aortic aneurysm repair (EVAR) compared to open aortic aneurysm repair, trials suggested that renal function may sustain greater deterioration after EVAR than after open repair.[1,2] Implicated factors include contrast-induced nephropathy (CIN), suprarenal endograft fixation, microembolization of renal arteries, and ischemia-reperfusion of the lower limbs.[1,3] The pathogenesis of CIN involves renal vasospasm, reduced blood flow to the outer renal medulla, activation of the tubuloglomerular feedback mechanism and oxidative stress.[2,4–7] Apart from general precautions, such as avoidance of hypoperfusion,[8] adequate hydration and avoidance of nephrotoxic drugs,[9] and use of low osmolarity contrast media,[10] current measures to prevent renal dysfunction following EVAR in clinical practice are lacking.[1]

Mannitol is an osmotic diuretic with antioxidant and renovascular effects that could preserve renal function after EVAR. However, the protective potential of mannitol in CIN is not clear and a randomized controlled trial of mannitol in EVAR has not been performed to date. Instead, mannitol has been used as part of a forced diuresis protocol, so that the effects of the individual components cannot be evaluated.[11,12] Moreover, dehydration due to inadequate replacement of urinary losses also could obscure any benefit. Furthermore, its protective potential has not been evaluated with the newer sensitive indices of renal injury such as cystatin-C and neutrophil gelatinase-associated lipocalin (NGAL).

To this end, the authors conducted this study to compare hydration versus hydration plus mannitol for prevention of renal dysfunction after EVAR. The authors evaluated creatinine, cystatin-C, and NGAL changes as well as more traditional markers such as urea and albuminuria.

MATERIALS AND METHODS

The research protocol was approved by the local ethics committee (No. protocol 429/17-12-09), and after written informed consent, 100 patients undergoing elective EVAR surgery were enrolled in the study (155 were assessed for enrollment in the study). Exclusion criteria (a priori exclusions) included patient refusal, end-stage renal failure (hemodialysis therapy) or 1 kidney, severe heart failure (left ventricular ejection fraction <25%), emergency surgery, known allergy to local anesthetics or mannitol, impaired coagulation or other contraindication to regional anesthesia, preceding angiography, embolism and embolectomy, and known renal artery stenosis or occlusion. Randomization was performed with the method of the closed envelope without block design (opaque envelopes prepared by A.P.), and the study was not blinded.

Patients received hydroxyzine, 50 mg, and ranitidine, 150 mg, orally the night before surgery. Diuretics and antihypertensive agents were omitted on the morning of surgery. In the operating room, after application of standard anesthetic monitoring and insertion of 2 large-bore intravenous catheters, ranitidine, 50 mg, diphenydramine, 4 mg, and metoclopramide, 10 mg, were administered IV, and an arterial catheter was placed for direct measurement of arterial pressure. Patients received hydration with 500 mL of Ringer's lactated solution prior to

*From the *2nd Department of Anesthesiology, †Department of Vascular Surgery; and ‡2nd Department of Clinical Biochemistry, Medical School, University of Athens, Attikon Hospital, Athens, Greece.*

Address reprint requests to Angeliki Pandazi, MD, PhD, Attikon University Hospital, 2nd Department of Anesthesiology, 1 Rimini Street 12462, Athens, Greece. E-mail: angpant@med.uoa.gr

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any other intervention. Afterwards, piperacillin-tazobactam, 4.5 g, and vancomycin, 1 g (or less, according to patient's creatinine clearance) (hourly infusion in 250 mL normal saline) infusions were instituted. Following standard procedures, the epidural space was approached in the sitting position in the lumbar region (L2-L4) with a Tuohy 18G needle, and an epidural catheter was placed either without or following a spinal injection with a 27G needle through the epidural catheter, according to the anesthesiologist's preference. The spinal injection included ropivacaine (Naropeine, Astra Zeneca, London, UK), 7.5 mg/mL, 1.8-2.2 mL and fentanyl, 20-30 μg, according to the patient's height. In the case of the epidural without spinal anesthesia, after a test dose of 3 mL of lidocaine, 20 mg/mL through the catheter, fentanyl 50 μg, and 10-15 mL of ropivacaine, 7.5 mg/mL, were administered, aiming for a sensory block up to T8-T10. If additional epidural doses were needed during the surgery, 3-4 mL of 7.5 mg/mL of ropivacaine were administered. Upon surgical incision, 0.5 g/kg of mannitol 20% (Mannitol, VIOSER S.A., Trikala, Greece) was administered in the mannitol group within 15 minutes. Further fluid management (after the initial 500 mL of lactated Ringer's solution) included the additional infusion of at least 2 mL/kg/h of lactated Ringer's solution and then further replacement of blood and urine losses. Colloids generally were administered when blood loss ensued (6% hydroxyethyl starch 130/0.4 solution [Voluven®, Fresenius-Kabi, Bad Homburg, Germany]) with a general rule of crystalloids:colloids 3:1, as generally is applied in the authors' institution. Red blood cells were administered if necessary to preserve blood hematocrit >28%. Mean arterial pressure was maintained within 80-120% of baseline values with infusion of phenylephrine or nitroglycerine if necessary. If urine output dropped below 0.5 mL/kg/h for 2 hours, furosemide, 5-20 mg, was given IV. Normal saline, sodium bicarbonate, or nonsteroidal anti-inflammatory drugs were avoided. Postoperatively, patients were monitored in the post-anesthesia care unit for at least 6 hours with 1-2 mL/kg/h hydration and the same goals as above.

Intraoperative recordings included heart rate, mean arterial pressure, arterial pH and hematocrit, hourly diuresis, administered fluids, total volume of administered contrast media, type of contrast media, hypotension (systolic arterial pressure <90 mmHg) or hypertension (systolic arterial pressure >150 mmHg) episodes with duration >10 minutes, the use of vasoconstrictors (phenylephrine or ephedrine) or vasodilators (nitroglycerine), type of endovascular stent (infrarenal or suprarenal), and duration of surgery (incision to last suture). In addition, major postoperative complications (hemorrhage, acute renal failure, reoperation) were recorded. The contrast media used was either iodixanol, 270 mg/mL (Visipaque®, GE Healthcare Biosciences, Princeton, NJ) or iobitridol, 300 mg/mL (Xenetix®, Guerbet, Aulnay-sous-Bois, France).

Peripheral blood and urine spot samples were collected just before the surgical incision (baseline) and at 24 and 72 hours after the end of the operation for measurement of serum creatinine, serum urea, urinary creatinine, and urinary urea (spot urine samples at 72 h were collected from spontaneous diuresis in sterile urine boxes). Blood samples were centrifuged at 2,500 rpm for 10 minutes, and the supernatants were stored at –80°C for further analysis. Serum creatinine also was measured at the time of followup. Neutrophil gelatinase-associated lipocalin (NGAL) was measured in urine by ELISA (HyCult Biotechnology, Uden, Netherlands), according to manufacturer's instructions. NGAL was measured in all patients at 24 and 72 hours and in 19 randomly selected patients at baseline (only for the NGAL measurement), and the values were corrected to urine creatinine.

Cystatin-C was measured in serum with a multiplex bead-based assay at 24 and 72 hours, using Milliplex Human Kidney Toxicity Panel 2 (HKTX2-38K, Millipore Corporation, Billerica, MA), according to the manufacturer's instructions. Serum samples were diluted 1:2,000 with assay buffer. The filter plate was prewashed with 200 μl of assay buffer on a plate shaker for 10 minutes at room temperature. Assay buffer was removed by vacuum, and then 25 μl of standards, controls, assay buffer and diluted serum sample were added into the appropriate wells, and 25 μl of the beads were added to each well. The plate was incubated with agitation overnight (16-18 h) at 4°C. Liquid was removed by vacuum. After 2 washes, 50 μl of detection antibodies were added and incubated for 1 hour at room temperature followed by the addition of 50 μl of streptavidin-phycoerythrin and incubation for 30 minutes. Finally, 100 μl of sheath fluid were added to each well and the beads were resuspended for five minutes on a plate shaker. The analysis was performed on the Luminex 200™ platform (Luminex Corporation, Austin, TX). The samples were batch analyzed for NGAL and cystatin-C at the end of the study period.

The primary outcome in the authors' study was serum creatinine values. Creatinine clearance was calculated according to Cockroft-Gault formula (creatinine clearance = (140 – age in years) × (body weight in kg) / (72 × S_{creat} in mg/dL) (× 0.85 for women) and fractional excretion of urea was calculated according to formula: Fe_{urea} % = (U_{urea} × S_{creat}) / (S_{urea} × U_{creat}), where U_{urea} = urine urea concentration (mg/dL), S_{creat} = serum creatinine concentration (mg/dL), S_{urea} = serum urea concentration (mg/dL), U_{creat} = urine creatinine concentration (mg/dL). Albuminuria was evaluated with the corrected albumin-to-creatinine ratio in urine. To evaluate the postoperative renal dysfunction in the first 72 hours after EVAR, the Risk-Injury-Failure-Loss-Endstage (RIFLE) criteria of creatinine and estimated GFR alterations were used.[13] The urine output criteria were not used since, in the authors' institution, oliguria and anuria are triggers for therapeutic interventions sooner than 6 hours and also because urine catheters are removed after 24 hours or less after EVAR.

Quantitative data were checked for normality of distribution with the Kolmogorov-Smirnov test. The minimum necessary number (total n = 84) of patients to assure a 0.80 power for creatinine values at 72 hours was calculated from an internal pilot study based on the authors' first 10 patients (Cohen's d = 0.31), who underwent exactly the same protocol as the other patients and subsequently were included in the final analysis without calculating any penalty for the power of the study. Normal distributed variables were analyzed with 1-way analysis of variance for between-groups comparisons and with repeated-measures one-way analysis of variance for within-groups comparisons. Non-normal distributed variables were analyzed with the Kruskal-Wallis and Mann-Whitney U tests for between-groups comparisons and with the Friedman's test for within-groups differences. Qualitative data were analyzed with cross-tabulation. Logistic regression for prognostic factors for renal risk/injury was carried out with the enter method and multicolinearity was checked. Correlations were checked with the Spearman's coefficient of correlation. The software used were SPSS v.15 and the G*Power v.3.1.5.

RESULTS

The protocol was abandoned in 11 patients due to conversion to general anaesthesia (n = 4), conversion of EVAR to open surgery (n = 2), persisting macroscopic hematuria due to urethral injury (n = 1), postoperative control of bleeding in the angiography suite (n = 2), and departure from protocol (n = 2) (without any analysis of the data). Additionally, 3 patients were discharged earlier than 72 h and were excluded due to missing data (exclusion of all data). In the final analysis, 86 patients were included. Data from followup measurements could be collected for 51 patients.

Age, sex, body mass index, ASA class, and time of followup of patients did not differ significantly between the 2 groups. Regarding coexisting diseases, arterial hypertension and diabetes mellitus were more frequent in the control group.