Normal Saline for Kidney Transplantation Surgery: Less Is More

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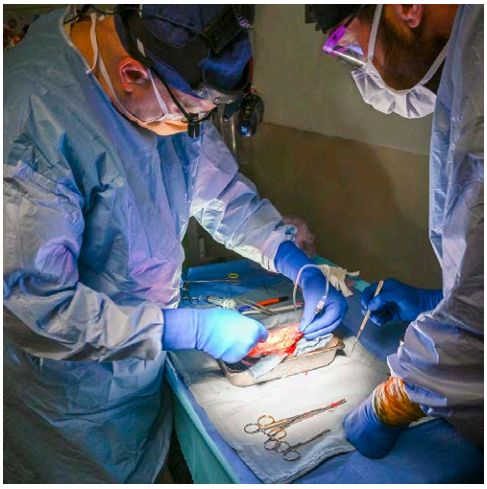
By 2030, 1 million people in the United States will have end-stage renal disease.[1] Kidney transplantation is a critically important intervention for these individuals: transplantation improves survival, quality of life, and healthcare costs compared to maintenance dialysis.[2–5] Regrettably, the supply of transplantable organs remains inadequate.[6] Hence, optimization of the short-term and long-term function of transplanted kidneys is critically important. Transplanted kidneys are vulnerable to acute kidney injury (AKI) related to hemodynamic instability,[7] hypovolemia,[8] immunologic injury, and ischemia-reperfusion injury.[9] After 25 to 30% of deceased donor kidney transplantation procedures in the United States, such perioperative AKI leads to delayed graft function,[10] which is typically defined as the need for dialysis within a week after transplantation.[9] This incidence is likely to increase even further with increased reliance on marginal kidneys from expanded criteria donors or donation after circulatory death. Delayed graft function has important long-term implications, with the risks of subsequent graft loss increased by 40%.[11] Since anesthesiologists are responsible for maintaining physiologic homeostasis during the perioperative period, they have an important potential role in preventing delayed graft function and thereby optimizing the function of transplanted kidneys.



"...anesthesiologists...have an important potential role in preventing delayed graft function and thereby optimizing the function of transplanted kidneys."

In this issue of Anesthesiology, Kolodzie *et al.* present a retrospective cohort study that evaluated the impact of an important facet of perioperative management, namely choice of crystalloid solution, on delayed graft function.[12] They found that administration of high proportions of normal saline (greater than 80% of crystalloid volume) in the operating room and postanesthesia care unit was associated with a 55% increased odds of delayed graft function. The finding was robust in sensitivity analyses that accounted for missing prognostic data, focused on deceased donor transplantation, and excluded patients who were not dialysis-dependent before surgery. The study has notable strengths. With 2,515 procedures and 485 primary outcome events, the cohort was sufficiently large for estimation of robust regression models. The investigators also efficiently assembled this cohort by linking electronic anesthesia records to the national Scientific Registry of Transplant Recipients, an approach worth repeating to evaluate other perioperative risk factors for posttransplantation outcomes. Conversely, there are several limitations. First, the overall strength of evidence for an association between proportion of normal saline administered and delayed graft function was not compelling ($P = 0.049$). Second, the cohort characterized care at a single large academic center in the United States, thereby raising concerns about its generalizability. Third, high proportions of normal saline were administered disproportionately in the early study period (2005 to 2009) *versus* the more contemporary period (2012 to 2015). Important changes in transplantation management (*e.g.*, immunosuppression regimens) occurred over this timeframe. Residual unmeasured confounding may therefore have contributed to the observed association between normal saline administration and delayed graft function. Fourth, modification of the definition of high-normal saline use to a volume-based threshold (greater than 2 1) led to its association with delayed graft

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function not meeting criteria for statistical significance (odds ratio, 1.48; 95% CI, 0.95 to 2.29; $P = 0.08$).

Should clinicians conclude that normal saline has significant risks with respect to delayed graft function after kidney transplantation? Replicability is a key aspect of scientific investigation,[13] yet the association between normal saline administration and delayed graft function has only been observed in the current study and a previous single-center cohort of 97 patients.[14] Thus, further research remains needed to establish whether the association is robust. Nonetheless, anesthesiologists should reasonably ask whether there are any compelling *advantages* to normal saline as the preferred crystalloid solution for kidney transplantation. The traditional rationale for prioritizing normal saline has been to avoid the theoretical risk of hyperkalemia induced by the potassium content (4 to 5 mEq/l) of balanced crystalloids.[15] Yet the assumption that normal saline reduces the risk of hyperkalemia is too simplistic. Instead, it may lead to a hyperchloremic metabolic acidosis that causes hyperkalemia. These unintended consequences have been observed in randomized trials and meta-analyses, where normal saline increased risks of acidosis and possibly hyperkalemia when compared to balanced crystalloids.[16,17] Based on these data, a recent consensus statement from the American Society of Anesthesiologists (Schaumburg, Illinois) states that "balanced crystalloid solutions are associated with a better metabolic profile" and "are therefore preferred" during kidney transplantation.[18]

In addition to direct evidence showing that normal saline does not prevent hyperkalemia in kidney transplantation, indirect evidence suggests that it can plausibly cause AKI. For example, administration of 2 l of normal saline as opposed to balanced crystalloid led to reduced renal artery flow and decreased renal cortical perfusion in a randomized crossover trial of 20 healthy volunteers.[19] Additionally, a randomized trial of 148 patients found that administration of 1.7 l of normal saline as opposed to balanced crystalloid during kidney transplantation led to lower intraoperative blood pressures and increased vasopressor requirements.[20] Consistent with these physiologic data, an increasing body of clinical evidence shows that normal saline leads to AKI in vulnerable patients. In the cluster crossover Isotonic Solutions and Major Adverse Renal Events Trial (SMART) of 15,802 critically ill adults (10.7% 30-day mortality risk), administration of normal saline *versus* balanced crystalloid led to an 8% relative increase in the risk of 30-day death, new dialysis, or persistent renal dysfunction.[21] In the cluster crossover Saline against Lactated Ringer's or Plasma-Lyte in the Emergency Department (SALT-ED) trial of 13,347 noncritically ill adults (1.5% 30-day mortality risk),[22] administration of normal saline *versus* balanced crystalloid led to a 20% relative increase in the risk of 30-day death, new dialysis, or persistent renal dysfunction. By comparison, in the alternating cohort Saline or Lactated Ringer's trial of 8,616 healthier adults (0.3% 30-day mortality risk) having colorectal or orthopedic surgery,[23] administration of normal saline *versus* balanced crystalloid had no significant effect on the risks of death and major complications. Median volumes of normal saline administered were relatively low (1 to 2 l) across these trials. Despite the low volumes, risks of AKI were consistently increased in higher-risk patients. Patients having kidney transplantation are arguably high-risk patients; hence, normal saline plausibly has negative impacts on kidney function after transplantation.

On balance, the *preferred* initial choice of crystalloid for kidney transplantation should be a balanced crystalloid solution. At the minimum, high-quality randomized controlled trial evidence suggests that this strategy will reduce risks of acidosis and possibly hyperkalemia. Will a strategy of prioritizing balanced crystalloids also prevent delayed graft function? Perhaps. The Better Evidence for Selecting Transplant Fluids (BEST-Fluids) trial, a large ongoing trial that aims to recruit 800 patients having decreased donor kidney transplantation, will eventually provide more definitive evidence to address this question.[24] Until such data are available, anesthesiologists should view the potential benefits of balanced crystalloids in preventing delayed graft function with some caution. Since delayed graft function has multiple underlying causal mechanisms, it is unlikely that modification of a single component of clinical care—substitution of balanced crystalloid for normal saline—will result in a meaningful reduction in the risk of delayed graft function. For example, substitution of balanced crystalloid for normal saline is unlikely to mitigate risks of delayed graft function within the context of coexisting hypotension or intravascular volume depletion. The choice of preferred crystalloid solution remains but a single component of the overall perioperative hemodynamic management strategy. Based on accumulating evidence on the adverse impact of intraoperative hypotension,[25] as well as the potential benefits of hemodynamic protocols to guide fluid and vasoactive medication administration,[26] multicomponent protocols are likely needed to offer any reasonable possibility of meaningful reductions in the risk of delayed graft function. Such protocols would certainly include a preference for balanced crystalloid, but also incorporate approaches to optimize cardiac preload and achieve individualized blood pressure targets. Anesthesiologists are ideally positioned to design, implement, and rigorously evaluate such multifaceted algorithms. Our profession should take this opportunity to improve outcomes in this very important patient population.

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