Host: Welcome to the *Anesthesiology* journal podcast, an audio interview of study authors and editorialists.

Dr. James P. Rathmell: Hello. I’m Jim Rathmell, Professor of Anesthesia at Harvard Medical School and Chair of the Department of Anesthesiology, Perioperative and Pain Medicine at Brigham and Women’s Hospital in Boston. I’m one of the Executive Editors of *Anesthesiology* and you’re listening to an *Anesthesiology* podcast that we’ve designed for physicians and scientists interested in the research that appears in our journal.

Today we’re going to talk with the lead author of an original research article and an accompanying editorial view that appear in the April 2020 issue. With us today is Dr. Kamal Maheshwari. Dr. Maheshwari works as an Anesthesiologist in the Liver Transplant Division and the Department of Outcomes Research at Cleveland Clinic in Cleveland, Ohio. Dr. Maheshwari is the first author on an article that appears in the April 2020 issue and it’s titled “Saline versus Lactated Ringer’s Solution: The SOLAR Trial.” Dr. Maheshwari, thanks for joining us.

Dr. Kamal Maheshwari: Thanks for having me.

Dr. James P. Rathmell: Also with us today is Dr. Dave Story. Dr. Story is Chair of Anesthesia at the University of Melbourne in Victoria, Australia. Dr. Story, he wrote an editorial view that accompanies Dr. Maheshwari’s research article and it’s also in the April 2020 issue and it’s titled “Intravenous Fluids Which Recipe?” Dr. Story, thanks for joining us and thank you particularly for staying up until midnight to join us for this recording.

Dr. David Story: Thank you very much, Dr. Rathmell and hello, Dr. Maheshwari.

Dr. Kamal Maheshwari: Hello, Dr. Story.

Dr. James P. Rathmell: Dr. Maheshwari, congratulations on completing a nice pragmatic study that addresses a question that clinicians face every day in our practices. So, let’s set the stage for the people listening. Both saline and lactated Ringer’s solutions are commonly given to surgical patients and saline has been associated with hyperchloremic acidosis and can cause other complications. What are the problems associated with use of a normal saline and in what settings have those problems been observed in previous studies?

Dr. Kamal Maheshwari: Normal saline or saline, as it’s commonly called, is widely used as a replacement fluid for over 100 years and we do know that saline composition is different from human plasma composition, specifically high chloride concentrations and saline will lead to, as you pointed out, hyperchloremic metabolic acidosis.

So, rightfully, the research community focused on identifying harmful effects of hyperchloremic metabolic acidosis, initial animal studies on worsening of kidney function, coagulation status, inflammatory response when saline was compared with other valid solutions like lactated Ringer.

But here’s the problem: researchers mostly use hemorrhagic animal models or sepsis models and gave 100 to 200 milliliters per kilogram of saline. In other words, a large amount of fluid was given to sicker animals.

Similarly, human studies are mostly performed in critical care or trauma settings; once again, in many small studies, sicker patients who require a large amount of fluid and worse outcomes with saline, especially more kidney injury or the need for Ringer replacement therapy.

And that saline got a rap, though, and many perioperative physicians stopped using it or advised not to use saline. However, most noncardiac surgery patients are generally healthy and they require much less fluid, as we noticed in the present trial.

This low fluid volume used during noncardiac surgery had never been convincingly associated with worse clinical outcomes such as renal dysfunction, coagulopathy or overall morbidity and mortality.

In fact, when we started SOLAR Trial in noncardiac surgery setting, only a retrospective analysis from Dr. Shaw’s group was available which showed worse outcome with saline. So, there was a huge need and interest in evaluating harmful effect of routine use of saline in noncardiac surgery setting.

Dr. James P. Rathmell: Well, that’s prefect. So, we have some animal data, we have some human data—kind of flawed human data that wasn’t in very healthy populations—that points to some problems with normal saline and you set out to do a much more pragmatic study of how we use these solutions every day. So, what was the hypothesis for your study?

Dr. Kamal Maheshwari: We conducted the SOLAR Trial, which is Saline or Lactated Ringer’s Trial, to determine the root of safety of lactated ringer and saline solution in patients having elective noncardiac surgery. We tested the primary hypothesis that a composite of major in-hospital postoperative complications would be lower in lactated Ringer’s solutions cohort.

Secondarily, we looked into the postoperative acute kidney injury and our hypothesis was that the acute kidney injury will also be less in patients receiving lactated Ringer’s solution.

Dr. James P. Rathmell: So, you set out to test the hypothesis that this composite of in-hospital mortality and major postoperative complications is less common in patients given the lactated Ringer’s than normal saline. We’re going to come back to this composite and explain it a little bit better. Tell us how the study was done.

Dr. Kamal Maheshwari: This was interesting. When I set out to answer this question in 2015, where we started thinking about this trial, I was just getting started to understand clinical trials and getting started on my research career in the Outcomes Research Department at Cleveland Clinic.

Looking at the comparatively low complication rate in noncardiac surgery settings, it was clear a large trial was needed but I was at that time not prepared to start a 10,000-patient trial.

After discussion with Dr. (Tesla), my mentor, I initially thought to move to some other question; however, he advised to consider a novel trial methodology which we have to test the feasibility of assigning intervention to the whole cohort or whole group of patients at any particular time period and then change to a different intervention and keep alternating it until we include enough patients for a meaningful analysis. And that was the start of it.

Dr. James P. Rathmell: So, pretty interesting. So, what you’re calling an alternating cohort controlled trial where you flip back and forth every couple of weeks from one intervention to the other; it’s not randomized, but it’s pseudo-randomized, I think, is where it would fall. Can you explain that design a little bit more and exactly how you carried it out?

Dr. Kamal Maheshwari: Essentially alternating intervention cohort trial can be used to test the difference between two interventions. When the interventions are part of a routine clinical care, the interventions are low risk and can be applied to the whole cohort or group of patients.

Another thing which is important for this trial design is there has to be some automated data capture. For example, we used ICD codes for assessing complications in our primary outcome and used creatinine lab values to assess our secondary outcome and both are automatically reported in electronically health records and our research database which shows up also within colorectal surgery because it gave us the model for the (sounds like: limb) and abdominal surgery which are common noncardiac surgeries and we had specific operating rooms for both services.

Operating rooms alternated between using either saline or lactated Ringer’s solution for two week’s period. For example, the first we did use normal saline, the second used lactated Ringer and so on for 36 cycles or a three-year period. As rightfully you pointed out, that’s not a randomized design, but the fluid choice, which was not randomized per patient, we did get two groups of people who had different exposure.

Patients were not informed for their group assignments, neither the investigator assessing the outcomes. Also, we have specified buildings for these two surgical settings which helped us ensure the patient received assigned intervention which is crucial for this trial design.
As we noted, we have 97% patients who received appropriate assignment and this was not accident; we ran an education program for all anesthesia staff: nurse anesthetists, residents, preoperative nurses and surgeons. So, it was a collaborative effort.

In the first six months we, in fact, made only assigned fluid available in the operating rooms. We ensured the night before the surgery that appropriate orders are there in the electronic health records. We made daily rounds in the operating rooms to ensure that appropriate fluid is given.

So, though this trial design is not randomized, we achieved different exposure in a different group of patients.

**Dr. James P. Rathmell:** So, what did you find?

**Dr. Kamal Maheshwari:** In more than 8,000 patients in which half of them received lactated Ringer’s solution and half received saline, on an average two liters of fluid was given to either group. The primary major complications happened in 5.8% of lactated Ringer group and 6.1% of normal saline patients and the difference was only 0.3%.

And there was secondary outcome postoperative acute kidney injury happened in 6.6% of lactated Ringer patients and 6.2% of normal saline patients. Again, the difference was minuscule: 0.4%.

The absolute difference between these treatment groups for each outcome were less than 0.5%, an amount that is not clinically meaningful.

I do want to point out that we did do multiple postop subgroup analysis. For example, at the patient with the history of diabetes or no history of diabetes or preoperative creatinine greater than 1.5% versus creatinine less than 1.5% or the patient receiving fluid less than 2 liters or 2-to-3 liters or greater than 3 liters. The relative risk of both primary and secondary outcomes were nonsignificant in all these analyses. In other words, the amount of fluid did not influence our conclusion.

**Dr. James P. Rathmell:** So, to go over that again, you enrolled a really impressive 8,616 patients and you saw no differences in this primary outcome. Again, a composite of in-hospital mortality and major postoperative renal, respiratory, infectious, and hemorrhagic complications, a composite outcome.

And then the secondary outcome of postoperative acute injury, no differences. And that held up throughout a number of different subgroup analyses. What were the limitations of your study?

**Dr. Kamal Maheshwari:** One of the primary limitations for this novel alternating intervention cohort design was that it’s not a true randomized controlled design and there’s always the risk of residual confounding.

We looked into both groups, first of all, that both groups are balanced in the baseline characteristics and based on absolute standardized differences, yes, they were balanced; but still, unknown confounding cannot be ruled out. So, that’s one of the major limitations.

Another limitation is for the primary outcome assessment we used International Classification of Disease codes reported in electronic health records as previously described by Dr. Shaw’s group and we know that even the best electronic records suffer from measurement and recording errors; however, we believe that such a random error would have influenced both groups and it is unlikely that it would change our conclusions.

Importantly, to validate the secondary outcomes in injury, we use well-validated Acute Kidney Injury Network criteria which is not from the ICD codes but for the actual creatinine lab value. So, our results or our conclusions we believe are valid.

And lastly, one of the limitations which we think that should be covered in the future trials is that we did not control the postoperative care of the patients and one might argue that the interoperative intervention could be diluted by the postoperative administration of various types of intravenous fluids.

However, it seems that our intervention of clinical interest, even if limited to intraoperative period, was substantial with median volume of 2 liters in merely four hours.

**Dr. James P. Rathmell:** So, what do you think the take-home message is for practicing anesthesiologists?

**Dr. Kamal Maheshwari:** It goes without saying that clinicians should use good clinical judgment in deciding appropriate fluid. Nonetheless, given what we learned from the SOLAR Trial, we can say that clinicians can reasonably use either solution, which is a saline or lactated Ringer intravenously in noncardiac surgery.

**Dr. James P. Rathmell:** Dr. Story, I want to turn to your editorial view. For listeners, again, the editorial’s titled “Intravenous Fluids: Which Recipe?” You do a nice job of putting this article into perspective. Your editorial reviews Dr. Maheshwari’s study and a few of these studies that were published earlier.

Dr. Maheshwari and his colleagues conclude their article by telling us: “Clinicians can reasonably use either fluid for routine vascular volume replacement in patients having noncardiac surgery.” It’s just what he told us a moment ago.

You then pose this question in your editorial: “So, can we now safely give saline to all noncardiac surgical patients, particularly higher-risk patients?” Of course the answer to that question depends on a number of factors. Can you walk us through how you think clinicians should think about choosing between saline and lactated Ringer’s?

**Dr. David Story:** Yes. The first thing I would like to say is that the SOLAR Study is a major contribution to the literature in this area. When we look at the decisions we make as clinicians, particularly in perioperative medicine, we start with the patient. So, the first question is, who is the patient we are caring for and do they have comorbidity, particularly as we’re discussing, do they have an incidence of kidney disease, particularly severe kidney disease, and other factors that may predispose them to adverse effects of fluid therapy?

Dr. Maheshwari correctly said that the studies have traditionally been done on sicker patients, so I think it’s important to think that we’re really talking about elective patients who are not having major blood loss and this is really maintenance fluid.

So, the question becomes, then, what operation is that individual patient having and are they likely to have significant blood loss? If that’s the case, then we’re talking more about resuscitation fluids and that, to my mind, is a different questions from one being asked in the SOLAR Study.

Another component is the actual volume given and the RELIEF Study that look at fluid volumes in major abdominal surgery which was conducted by the anesthesia and intensive care research networks in Australia and New Zealand, and our friends at Cleveland Clinic made a contribution to that study, found that contrary to the hypothesis, that larger volumes had less acute kidney injury. Again, like the SOLAR Study, there was no difference in the overall primary endpoint, but there’s less acute kidney injury in patients having larger volumes.

The importance of that is that if that were to sway where practice is going, it would mean that patients in the intraoperative period may have close to 3.5 liters rather than 2 liters over the intraoperative period, so after four hours. But importantly, if we go out to 24 hours, we’re looking at more like about 6 liters rather than 3 liters and I think that’s a major difference in volume that patients would be getting.

So, my view is that I’m a bit more cautious about where we should go with the information that the SOLAR Study provides us, but I agree that there – at one end of the spectrum we have relatively healthy patients having elective surgery but as patients become sicker and the volumes required increase, I am a bit more reluctant to recommend using saline at this point.

**Dr. James P. Rathmell:** Well, I think you’ve told us a lot of this, but I want to go over it again. What do we really know for certain about the
risks of metabolic acidosis and kidney injury associated with these two intravenous fluid formulations?

**Dr. David Story:** Right. What we do know is that if you give patients even moderate volumes of saline, then there was a signal within the SOLAR Study towards this, that you get a hyperchloremic metabolic acidosis.

Now, if you follow the Stewart approach for acid-based disorders, that’s a very easy phenomenon to understand that the plasma chloride increases because the chloride and content in plasma is only about 105 millimole per liter and in saline is 150 or 154 millimole per liter. So, there’s quite a marked rise in chloride reducing the difference between the sodium and the chloride and you get an acidosis.

And if you follow the bicarbonate-based approach, it’s (inaudible)-based, this would be a classic narrow anion gap metabolic acidosis. So, this phenomenon in well-known.

One concern about this is that clinicians using saline, particularly larger volumes, need to be aware that this will happen and they don’t become concerned that there’s a metabolic acidosis that is suddenly appearing that they aren’t anticipating. So, it needs to be anticipated.

The question then arises, is this clinically important? The answer is probably that a minor hyperchloremic metabolic acidosis is not all that clinically important; however, if there’s an existing metabolic acidosis and the patient is receiving resuscitation volumes of saline, it is quite possible that that acidosis will be aggravated and that may further undermine protein, structure and function within patients.

One of the complexities of acid-based disorders is that often there is an underlying pathological process producing particularly metabolic acidosis in critically ill patients and trying to tell them what’s the process and what’s directly due to the acidosis is harder.

So, we do get this acidosis. It is probably of limited importance in healthy patients getting maintenance fluids, but it, a), complicates the picture of managing higher volumes; and, may further undermine the acid-based status of someone who’s becoming increasingly unwell.

Dr. James P. Rathmell: In your editorial you sum things up very nicely by posing another question: “Would I now give saline to a typical patient in my anesthesia practice: a 70-year-old with hypertension, diabetes, mild chronic kidney disease for a sigmoid colectomy, while planning more liberal fluid volumes?”

Take us through the rationale you used to answer your own question.

**Dr. David Story:** As I mentioned earlier, I have greater uncertainty about the final answer to this question. At this time, I would not be keen to give this sort of patient – which is, in fact, the typical patient I care for every day, I would not be keen to give them saline for this type of surgery. I’m concerned that there’s still a possibility that this patient may develop acute kidney injury, that the acidosis will be aggravated if they do develop an acidosis.

What I think is still required is probably a definitive trial of blinded fluid administration. The one that I think Dr. Maheshwari much earlier mentioned just appeared so incredibly daunting. Yes, it is hard work, but to my mind this is such a fundamental question.

If we prove beyond reasonable doubt that saline is safe to give to even relatively unwell patients in routine surgeries, that would be a major change in practice. At my hospital, we routinely use what we would call Hartmann’s solution, but basically is a close cousin of lactated Ringer’s. And worldwide we would be looking at having basically a cheaper fluid being as good as the other fluids that we use.

So, my view is that I would like to see a large multicenter international trial trying to answer this question.

**Dr. James P. Rathmell:** Dr. Maheshwari, tell us a little bit about where you are in your career and what comes next for you and your research team.

**Dr. Kamal Maheshwari:** I’ve been fortunate to be an anesthesiologist at Cleveland Clinic for the last 10 years. Actually, I started my research career five years back at Outcomes Research Department with this sort of trial idea. So, I’m fortunate, but this trial also shows me that this research is very humbling because when I started I thought that it was slam dunk that saline is bad.

I’ve also worked on many questions like role of multimodal pain management, the role of different inhalation agents like isoflurane versus sevoflurane or radius and (inaudible) anesthesia techniques to help guide perioperative management and fluid outcomes.

And as Dr. Story mentioned, that working with Outcomes Research Department, we work collaboratively in many large fluid management trials. For example, a crystalloid and colloid (inaudible) liver which is the RELIEF Trial.

Currently my work is focused on testing predictive algorithms or fluid management and blood pressure management and we recently completed a randomized controlled trial on using hypertension prediction index guidance for blood pressure management. And another trial which recently finished using assisted fluid management software which was a single-arm multicenter trial and I’m eager to share the results with you all soon.

Also, I’m hoping to generate enough excitement around testing different colloids which is starches versus albumin in noncardiac surgery. So, a lot of ideas and a lot of work to do.

**Dr. James P. Rathmell:** Terrific. I hope today’s discussion will lead many of you who are listening to read this new article and the editorial view that appear in the April 2020 issue of Anesthesiology where you can learn more about the longstanding controversy over complications associated with intravenous crystalloid administration during surgery.

Dr. Jon Wanderer from Vanderbilt and I also created an infographic that appears in the same issue and it’s titled “The Great Fluid Debate 2020” where we aim to place the major findings of this study in perspective with the previous studies about saline and lactated Ringer’s.

Drs. Maheshwari and Story, thank you for joining me today and for the terrific explanations.

**Dr. David Story:** Thank you very much.

**Dr. Kamal Maheshwari:** Thank you very much.

**Host:** You’ve been listening to the Anesthesiology Journal podcast, the official peer-reviewed journal of the American Society of Anesthesiologists. Check anesthesiology.org for an archive of this podcast and other related content.