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

Dr. BobbiJean Sweitzer: Hello, I’m BobbiJean Sweitzer, Professor of Anesthesiology at Northwestern University and an Associate Editor for Anesthesiology. And you are listening to an Anesthesiology podcast designed for physicians and scientists interested in the research that appears in our journal.

Today we are speaking with the author of a publication that appears in the January 2018 issue of the journal. With us is Dr. Alexandre Joosten. Dr. Joosten is the lead author of an article titled, “Crystalloid versus Colloid for Interoperative Goal-directed Fluid Therapy using a Closed-loop System: A Randomized, Double-blinded Controlled Trial in Major Abdominal Surgery.”

Dr. Joosten is an Assistant Professor in the Department of Anesthesiology at Erasme University Hospital, Universite Libre de Bruxelles in Brussels, Belgium. Welcome, Dr. Joosten.

Dr. Joosten: Hello, Dr. Sweitzer. Thank you for the invitation.

Dr. Sweitzer: I hope I didn’t completely butcher your name or your institution’s name. And if you want to introduce yourself again with your perfect accent, please go ahead and do that.

Dr. Joosten: No, it’s okay.

Dr. Sweitzer: Thank you. So, can you summarize what you intended to with this study?

Dr. Joosten: The type of fluid and volume regimen given intraoperatively can both impact patient outcome after major abdominal surgery. Our study tested the hypothesis that when using a closed-loop assisted, goal-directed fluid therapy, balanced colloids are associated with fewer post-op complications compared to balanced crystalloids in this population.

Dr. Sweitzer: And why was this important for them to be aware?

Dr. Joosten: Multiple studies have shown that goal-directed, fluid therapy strategy based on the optimization of flow-related variables represent the best approach for fluid titration in high-risk surgical patients.

Unfortunately, adoption and implementation of this strategy has tended to be low among providers due to high workload and attention required for consistent application, resulting in significant variability in practice.

To address this problem, our team has developed a closed-loop system for fluid administration in order to assist providers in consistently applying goal-directed, fluid therapy strategies in the operating room.

The developed system has demonstrated feasibility and efficacy across a variety of clinical scenarios. It delivers three boluses using a standardized protocol and then can maintain nearly 100% compliance and remove provider variation as one of the main values for patient care.

Dr. Sweitzer: So, once again humans are the weak link or the variable that needs to be controlled for.

Dr. Joosten: Yes, exactly. Humans induce a lot of variability. That’s what we try to avoid.

Dr. Sweitzer: So, how was this closed-loop system used for this particular study?

Dr. Joosten: Using our closed-loop system for goal-directed fluid therapy allowed us to specifically study the impact of the fluid administered on patient outcome since the system would be free from both variation in practice and in compliance to the goal-directed fluid therapy protocol.

Dr. Sweitzer: Did the anesthesiologist know when the closed-loop system administered fluid?

Dr. Joosten: Yes. Visual and audio alerts were created for each fluid bolus to ensure the anesthesiologist was aware of each intervention.

Dr. Sweitzer: And why was this important for them to be aware?

Dr. Joosten: So that the anesthesiologist can see and know where fluid bolus is delivered to the patient and, so it can interact or be a participant for the case or it keeps the anesthesiologist in the loop.

Dr. Sweitzer: I understand. So, can you tell us more about the fluids that you used: the type, the quantities?

Dr. Joosten: Yes. So, volume of fluids were administered according to two distinct objectives: the first one was to cover baseline patient requirements. This was achieved by a continuous infusion of an isotonic balanced crystalloid infusion—Plasmalyte®—set at the rate of 3 ml/kg/hr via an infusion pump.

The second one was to optimize flow-related variables according to the goal-directed fluid therapy. This was achieved by repeated boluses of 100 ml of either a balanced crystalloid solution or balanced colloid solution, namely a 6% tetrastarch solution—Volulyte®.

Both solutions were administered in a blinded fashion. Importantly, an upper limit daily dose of 33 ml/kg of both study fluid for this indication was defined. If the upper limit of the study fluid was reached, unblinded Plasmalyte® was used thereafter consistently in all patients.

Dr. Sweitzer: So, how did you decide on the 100-ml quantity for fluid boluses using this closed-loop system?
Dr. Alexandre Joosten: So, working with different bolus sizes and performance of the controller, we observed that using boluses of 100 ml was the right balance between the information content in bolus response and minimizing fluid delivered.

Splitting a single 200-ml bolus into two 100-ml boluses provides the control with two feedback data points instead of just one, improving future performance, and reducing total administered volume.

In addition, some recent studies have demonstrated that 100-ml fluid challenges are indeed able to predict fluid-responsiveness.

Dr. BobbiJean Sweitzer: And I guess one of the reasons perhaps we humans use a larger bolus is there’s less work in that, right? You give one intervention gives you twice as much and so you just have half the amount of work.

Dr. Alexandre Joosten: Uh-huh [affirmative].

Dr. BobbiJean Sweitzer: But the machine didn't care whether it's doing it.

Dr. Alexandre Joosten: That's right. But we decide as it’s also a prototype to use smaller boluses and the system is going to learn from each bolus that is given to the patient and then for us it’s much more correct to use smaller fluid boluses.

Dr. BobbiJean Sweitzer: And more granular information. Like you said, double the amount of data points you’re getting, actually, back.

So, what were the primary outcome measures of this study of yours?

Dr. Alexandre Joosten: Having standardized the volume of fluid given through the closed-loop system, we studied the impact of the type of fluid on patients’ post-operative outcome.

For this purpose, we chose the Post-Operative Morbidity Survey goal or POMS score at post-operative day two [POD2].

Dr. BobbiJean Sweitzer: Tell us a little bit more about the POMS or the Post-Operative Morbidity Survey score. Can you explain more what this consists of and how it is determined?

Dr. Alexandre Joosten: Yes. So, the score includes nine domains for which patients were assessed for diagnostic features: pulmonary, infectious, renal, cardiovascular, gastrointestinal, neurological, hematomaternal, wound and pain.

This score has been validated and used in a wide range of elective moderate and major surgeries and we determined the score on the morning of the second post-operative day [POD2] because the impact of fluid balance is mainly observed as this moment.

Dr. BobbiJean Sweitzer: What other outcomes did you measure?

Dr. Alexandre Joosten: Other outcomes were the incidence of major and minor post-operative complications up to 30 days after surgery.

Dr. BobbiJean Sweitzer: Can we dive a little bit deeper into the details of the types of surgeries, the patient characteristics, especially if there were any differences between the two fluid groups that you were comparing?

Dr. Alexandre Joosten: By protocol, we included only adult patients scheduled for open major abdominal surgeries lasting at least three hours in our prospective randomized controlled trials.

So, we included pancreatectomy, cystectomy, aortic surgery, gastrectomy, major gynecological procedure, nephrectomy, colectomy and other types of surgery.

Dr. BobbiJean Sweitzer: And how many patients did you enroll in each group?

Dr. Alexandre Joosten: Yes, we included 160 patients; so, 80 patients per group.

Dr. BobbiJean Sweitzer: So, how was unexpected bleeding or hypotension managed when it did not respond to the fluid at the liver via the closed-loop system?

Dr. Alexandre Joosten: Yes, management of unexpected bleeding or hypotension was defined also by protocol. So, the anesthesiologist in charge of the patient had also the opportunity to administer additional balanced crystalloid without using our closed-loop system. So, this was a rescue fluid.

In addition, if he felt that patient was fluid-optimized, but mean arterial pressure remains low, like below 65 despite an appropriate anesthetic depth, he was allowed to administer vasopressors in order to optimize blood pressure.

Importantly, the closed-loop system delivers only 100-ml fluid boluses over six minutes; this system is, therefore, clearly not designed for acute bleeding resuscitation, but rather fluid optimization in line with goal-oriented fluid therapy protocols.

Dr. BobbiJean Sweitzer: Did your study protocol dictate the post-operative fluid management or was this just confined to the interoperative care with the patient?

Dr. Alexandre Joosten: Once again by protocol, the post-operative maintenance fluid for all patients was 1.5 ml/kg/hr of 5% dextrose saline and if additional volume was required, isotonic crystalloid was administered at the discretion of the physician in charge of the patient.

Dr. BobbiJean Sweitzer: So, you used the statistical test that I personally am not familiar with, the Kolmogorov-Smirnov Test. I think I’ve butchered that name as well, but can you explain the need for this to me in layman’s terms or what this particular test is about?

Dr. Alexandre Joosten: Yes. This test allows us to assess the distribution of data. Other tests that could have been used for this purpose are the Anderson-Darling or the Shapiro-Wilk Test.

Assessing the normality or non-normality of the distribution was required for future statistical analysis of our data.

Dr. BobbiJean Sweitzer: Did you find a difference in the outcomes you were looking at between the patients who received either colloids versus crystalloids?

Dr. Alexandre Joosten: Yes, primary outcome, the POMS score, on post-operative day two [POD2] was significantly lower in the colloid group compared to the crystalloid one. In addition, incidence of major
and minor post-operative complications were also significantly lower in the colloid group. These results were associated with a lower intraoperative fluid balance with the balanced colloid, essentially due to a lower fluid volume administration.

**Dr. BobbiJean Sweitzer:** So, just to clarify, a lower POMS score is better?

**Dr. Alexandre Joosten:** Yes, the lower, the better.

**Dr. BobbiJean Sweitzer:** Uh-huh [affirmative], so everything pointed to the benefits of colloids versus crystalloids.

**Dr. Alexandre Joosten:** Yes. And everything seems to be linked to each other.

**Dr. BobbiJean Sweitzer:** Uh-huh [affirmative]. So, did you find a difference in the performance of the closed-loop management between the two groups?

**Dr. Alexandre Joosten:** Yes, by protocol, because it’s a double-blinded, randomized control trial, closed-loop management between the two groups could not be different.

In addition, the number of fluid boluses delivered manually through the closed-loop system by the anesthesiologist in charge of sedation was not different between the two groups.

In most of the cases, the reason for additional fluid was acute bleeding.

**Dr. BobbiJean Sweitzer:** I understand. So, how do the findings of this study compare to others that have been published?

**Dr. Alexandre Joosten:** So, only two prospective randomized, double-blinded studies have compared the efficacy of colloids and crystalloids when using a goal-directed approach for fluid management in patients undergoing abdominal surgery.

In the first study, Yates and colleagues report no perioperative benefit of colloids over crystalloids in terms of complications and need of vasopressors in more than 200 patients undergoing colorectal surgery despite a lower amount of fluid required.

They used a continuous cardiac output also to standardize and guide fluid therapy in their patients; however, 38% of patients in the crystalloid group received a rescue colloid which was a modified gelatin solution compared to 12% in patients in the colloid groups.

As a result, in fact, this trial compared two groups which received a combination of crystalloids and colloids in different proportion.

In the second study, Feldheiser from Germany reported that the balanced colloids solution was associated with a higher stroke volume and the lower volume of fluid administered in 50 patients undergoing ovarian cancer surgery.

In this study a goal-directed fluid therapy protocol was also applied using the esophageal doppler. However, as it was a very small pilot study, the trial was underpowered to assess the effects of study fluids on postoperative complications and a hospital length of stay [LOS].

These two previously published studies comparing balanced crystalloids to balanced colloids—when combined together—together suggests that balanced colloids induce a larger volume extension effect compared to crystalloids and as a result, less volume of colloids were needed to achieve a comparable hemodynamic endpoint.

As no clear outcome benefit emerged from the previous studies, no recommendation on the use of colloid over crystalloid in the perioperative period could be made.

Our study makes a much stronger connection between fluid type, of optimizing physiological variables, and improving clinical outcome. Moreover, the use of a closed-loop system to remove intervention bias between groups is a feature that has not previously been possible in comparing fluid.

**Dr. BobbiJean Sweitzer:** Can we talk a little bit more, though, about do we really need a machine to do something this seemingly straightforward as providing intravenous fluids? Are these advantages of a closed-loop system worth the cost versus perhaps just training humans or having humans be more – follow protocols?

**Dr. Alexandre Joosten:** So, once again, goal-directed fluid therapy strategies have been shown to benefit moderate- to high-risk surgical patients and have recently been recommended by professional societies in the United Kingdom, in France, and in Europe.

However, despite the growing evidence, these strategies are often not implemented in current practice. One of the reasons for this lack of implementation is that goal-oriented fluid therapy strategies, like any other complex clinical protocol, require significant provider attention and vigilance for consistent implementation.

And it is well-known that even under strict study conditions, protocol compliance rates are also not greater than 50%. And so, to address this problem, we have developed a closed-loop system for goal-directed fluid therapy administration.

Another thing is that computer systems excel at repetitive attention-based tasks and do not suffer from vigilance decrement. For this reason, closed-loop or automated systems frequently exhibit higher accuracy in maintaining a target set point compared to clinicians.

**Dr. BobbiJean Sweitzer:** We’ve shown this in non-medical settings, as you mentioned with some examples early on. So, it was just a matter of time, I think, until we started to show these kinds of benefits in the medical practices.

I recall that your registered protocol indicates that you intend to follow this cohort of patients out to a year, one year, and measure long-term outcomes. Can you tell us a little bit more about what we can look forward to?

**Dr. Alexandre Joosten:** Yes. So, our last patient was included in December 2016. So, accordingly we’d be able to analyze renal function and long-term quality of length for the end of this year and we will publish results very soon.

**Dr. BobbiJean Sweitzer:** And you’ve had good follow-up of the 160 patients?

**Dr. Alexandre Joosten:** Yes, it’s to us quite okay. So, we had the biology, so the renal function on the medical records. And when we don’t have it, we call the medical practitioner of each patient in order to have this measure. And for the quality of life, it was on a call confirmed with the patient.

**Dr. BobbiJean Sweitzer:** Excellent. We look forward to seeing that. Do you believe technology such as what you used to manage fluids during this study have a role outside of the operating theater, like in the ICUs or just simply on the floor with patients?

**Dr. Alexandre Joosten:** Certainly, for fluid administration, it can have a place in the post-operative care of high-risk patients; you have to know it
so that closed-loop system for vasopressor infusion and glucose control has already been successfully evaluated in animals and human studies. So, it should be yes, I think.

Dr. BobbiJean Sweitzer: Uh-huh [affirmative]. Do you predict when closed-loop systems, such as the one you used, are routinely used to manage fluids?

Dr. Alexandre Joosten: We think this technology should become the standard of care for high-risk patients. The key element will be the acceptance of clinicians, of course. They have to be convinced that closed-loop systems are not designed to replace them, but rather help them in managing patients in their daily activity.

Dr. BobbiJean Sweitzer: Is there a practical point from your study that one of our listeners can apply to their patient care even if they do not have a closed-loop system available currently?

Dr. Alexandre Joosten: Yes. Independently of the closed-loop system, our study shows the interest for the patients of administering fluid according to an algorithm with predefined therapeutic targets allowing individualized management.

Dr. BobbiJean Sweitzer: Is there anything else you'd like to add or clarify?

Dr. Alexandre Joosten: No, it’s quite okay. I think if you are able to show the picture or the video of the closed-loop system—it was taken during a case—that could be nice because if they have a look on our previous publication, we have a published paper with a nice picture of it.

Dr. BobbiJean Sweitzer: Is this system relatively simple and easy to set up?

Dr. Alexandre Joosten: It’s easy. I think it needs attention at least to be familiar. The problem for us for daily routine is that it takes a lot of place because you already have your anesthesia workstation and you have to think that you have a hemodynamic monitor that exists that you can use and buy.

And then I have to add a table and I have two other computers on the table, two other pumps and infusion lines. So, it can take some place for the – in the operating room.

And so, in some operating rooms maybe when you don’t have a lot of place for the anesthesiologist, then it can be a problem.

So, the goal for us in the future would be to integrate the system into the anesthesia workstation.

Dr. BobbiJean Sweitzer: Thank you. So, I hope today’s discussion will interest many of our listeners and lead you to read this important article to learn more.

Thank you, Dr. Alexandre Joosten, for discussing your work with us today. I wish you well as you continue your efforts to enhance the practice of anesthesiology and strive to improve the care of our patients.

Dr. Alexandre Joosten: Thank you very much.

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