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EDITORIAL

A global perspective on acute kidney injury after major surgery: much needed insights and sobering results

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Acute kidney injury (AKI) is an abrupt decline in kidney function occurring within hours or days. In patients having surgery, postoperative AKI is a major complication associated with adverse outcomes including mortality [1]. Postoperative AKI is common but reported incidences substantially vary [2]. Zarbock and colleagues [3], with an international observational study on more than 10,000 patients, now provide much needed insights into the incidence of postoperative AKI in patients having major surgery.

The findings of the study are sobering. About 1 in every 5 patients having major surgery requiring postoperative treatment in an intensive care or high-dependency unit developed AKI according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria within the first three postoperative days. Postoperative AKI occurred most frequently in patients having urological, cardiac, vascular, and general surgery (and not so frequently in patients having neurosurgery or orthopedic surgery). Although two-thirds of patients had 'only' stage 1 AKI, one-third of patients had persistent AKI (defined as AKI lasting for more than 48 h). Additionally, although most patients had low severity and short duration of AKI, postoperative AKI was associated with a fivefold higher risk for in-hospital mortality.

A strength of the study is that urine output was considered for AKI diagnosis, while most previous studies only considered creatinine criteria. Another strength is the documentation of rapid reversal and persistent AKI as well as the relevant composite long-term outcome major adverse kidney events at day 90 that occurred in about 20% of patients developing postoperative AKI. Finally, the study provides a global perspective on postoperative AKI, with about half of the patients recruited in Europe and about a third in Asia. About 10% of patients were included in African countries, and close to 2% in North America.

To potentially avoid postoperative AKI, identifying modifiable risk factors for its development is important. Besides non-modifiable baseline risk factors such as older age, comorbidities, and type of surgery, the study identified risk factors amenable to changes in perioperative management, including use of vasopressors and aminoglycosides. Interestingly, intraoperative hypotension was not an independent risk factor for postoperative AKI, yet the use of vasopressors was.

The lack of statistical association between intraoperative hypotension and postoperative AKI in the study by Zarbock and colleagues [3] does not discount the importance of perioperative blood pressure control. In contrast to this study, previous registry studies clearly established intraoperative hypotension as a modifiable risk factor for postoperative AKI [4]. As the population harm threshold for postoperative AKI is a mean arterial pressure of 60–70 mmHg, it is generally recommended to maintain mean arterial pressure above 65 mmHg [4]. As preoperative baseline blood pressure varies [5], intraoperative hypotension harm thresholds may also differ among individual patients having surgery. It remains unknown though whether the relation between intraoperative hypotension and postoperative AKI is causal because there are only few randomized trials on the

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effect of targeted blood pressure management on postoperative renal function. Maintaining mean arterial pressure at ≥ 75 mmHg compared to at ≥ 60 mmHg did not reduce the incidence of postoperative AKI within 30 days after surgery in major non-cardiac surgery patients [6]. Individualized—compared to routine—blood pressure management reduced renal risk and injury (according to RIFLE criteria), but not renal failure, in patients having major non-cardiac surgery in the INPRESS trial [7]. The ongoing GUARDIAN (NCT04884802) and IMPROVE-multi (NCT05416944) trials will provide further evidence whether targeted intraoperative blood pressure management can help to reduce postoperative AKI.

Beyond blood pressure control, small trials suggested that goal-directed—mainly cardiac output-guided—hemodynamic therapy may help to reduce the risk for AKI [8, 9]. However, the largest trial to date, the OPTIMISE II trial, revealed that maximizing stroke volume using fluids and dobutamine does not reduce the incidence of postoperative AKI (OPTIMISE II trial [10]; presented at EBPOM World Congress of Prehabilitation Medicine 2023 in London on July 6, 2023).

Clinicians routinely give vasopressors and fluids to 'optimize' hemodynamics during surgery. However, vasopressors themselves may promote postoperative AKI [11]. In the study by Zarbock and colleagues [3], the use of vasopressors was associated with a 1.8-fold increased risk of developing postoperative AKI. However, the use of vasopressors should not be interpreted as the cause of AKI and it seems unwise to postulate that vasopressors should be avoided. Whether the use of vasopressors is a surrogate for suboptimal hemodynamic status or whether they directly affect renal function cannot be answered in this study.

Optimal perioperative fluid therapy to prevent AKI also remains unknown. Regarding the amount of fluid, fluid overload, on the one hand, will compromise kidney function by increasing venous congestion and hemodilution. On the other hand, the RELIEF trial [12] showed that restrictive—compared to liberal—perioperative fluid management resulted in more AKI in patients who had major abdominal surgery. Regarding the type of fluid, the use of hydroxyethyl starch containing fluids is associated with AKI in critically ill patients. In patients having elective surgery, the association between hydroxyethyl starch and AKI is less clear.

Several studies suggested that the use of an 'AKI bundle' in at-risk patients can help to decrease AKI rates [13]. AKI bundles proposed in the literature substantially differ, but typically consist of a group of measures aimed at improving hemodynamics and minimizing exposure to nephrotoxic events in patients who were identified by a biomarker to be at high risk for AKI. Currently, Zarbock and colleagues are conducting a trial testing the hypothesis that a KDIGO-based bundle intervention reduces stage 2 and 3 AKI within three days after major non-cardiac surgery compared to routine care (NCT04647396).

Another remarkable finding in the study by Zarbock and colleagues [3] is the striking difference in the incidence of AKI by region, with a 5.6-fold difference between the highest (North America) and lowest (Africa) incidences. These differences in AKI incidence remain unexplained but presumably result from differences in AKI screening, patient baseline risk, and types of surgery. It is notable though that failure to rescue rates also differed substantially among regions: mortality was highest in regions with the lowest AKI incidence. This suggests that outcomes from AKI are amenable to intervention, and that the lack or inadequacy of intervention is a driving factor for mortality. It may, thus, be wise to invest more resources in reducing rates of failure to rescue and progression from acute to chronic kidney disease to improve long-term survival among patients with postoperative AKI. These resources may include systematic kidney health assessments after surgery, routine postoperative rounds for high-risk patients identified pre- and intraoperatively, and continuous postoperative monitoring [14, 15].

Identifying interventions to avoid postoperative AKI and reduce progression from acute to chronic kidney disease remain key challenges for future perioperative research. In the meantime, it seems prudent to avoid restrictive or zero balance perioperative fluid regimens [12] and to optimize intraoperative hemodynamics [8, 9].

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