EDITORIAL

Transplanting the Liver for a New Life: Can the Kidney Throw in a Spanner?

Narayanan Parameswaran

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Department of Paediatrics, Jawaharlal Institute of Postgraduate Medical Education & Research, Puducherry, India

Corresponding Author: Parameswaran N, Department of Paediatrics, Jawaharlal Institute of Postgraduate Medical Education & Research, Puducherry, India, Phone: +91 9443458850, e-mail: drnarayananp@gmail.com

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Acute kidney injury (AKI) is a known predictor of poor outcomes in critically ill children in most settings.[1,2] Hence strategies to prevent or mitigate the risk factors for AKI have been of great interest to clinicians and researchers. The various reported risk factors result in AKI through one of the known common mechanisms including ischemia, drugs and toxins, immune dysregulation, etc. Among the various risk factors commonly encountered, drugs and toxins are comparatively easier to identify and deal with in the acute setting. But many complex mechanisms can lead to both ischemia and immune dysregulation and hence identifying and modifying these risk factors remains a challenge. Children undergoing solid organ transplantation are not exempted from these challenges. Acute kidney injury has been known to occur in nearly half the children undergoing liver transplantation (LT).[3] The additional risk factors in this subset of children involve issues unique to children with acute liver failure (ALF), including the presence of high levels of bilirubin and other metabolites in the blood, hepatorenal syndrome, increased chances of an ischemic hit during the perioperative period, use of drugs like tacrolimus with known hepatic toxicity and immune dysfunction leading to a heightened risk of infections, etc. The various risk factors reported in the literature include preoperative total bilirubin level, presence of ascites, lower postoperative jaundice clearance, increased intraoperative blood loss, increased time of the anhepatic phase, etc.[4–6]

In this context, the retrospective observational study by Demiroz D et al., in this issue of the journal tried to evaluate the factors that may cause AKI in pediatric LT patients and to investigate the effects of AKI on mortality and length of hospital stay.[7] They performed a retrospective review of LT patients under the age of 18 between the years 2015 and 2021 and identified 235 patients meeting their inclusion criteria. The sample size is good enough to draw reasonable conclusions and is one of the highest compared to other reports.[4–6] The authors of the present study observed that 60 (25.5%) of their patients developed AKI during the post-operative period.[7] The frequency of occurrence of AKI reported by Demiroz D et al. seems significantly less compared to what has been reported in the past. The authors have attributed this to the fact that they excluded children with pre-existing renal dysfunction. But in their series, Zhang Y et al. also excluded children with chronic kidney disease (CKD) and found that 47.5% of children developed AKI after LT.[4] This significantly lower occurrence of AKI reported by Demiroz D et al. is intriguing. From the available data provided by Demiroz D et al., the clinical profile of their children does not seem to be significantly different from previous reports. But, it is possible that if we look deeper, we may find significant differences in the clinical details like etiology and severity of underlying liver disease, preoperative stabilization, and perioperative management (drugs used, type of anesthetic agents, duration and complications of surgery, etc.,). Another possibility is that in a retrospective series like this, data retrieval can be suboptimal. In fact, Demiroz D et al. had excluded 36 patients due to lack of data. If most of these excluded children had AKI, the results would have been significantly different.

The risk factors for AKI reported by Demiroz D et al. are along expected lines. They found that prolongation of warm ischemia time and operation time were independent predictors of AKI.[7] They also reported that long operation time and intraoperative blood transfusion increased the severity of AKI. All these risk factors can lead to ischemic insult to the kidneys and the mechanism seems straightforward. The need for intraoperative blood transfusion may be a surrogate marker for hypovolemia and hemodynamic compromise during surgery, leading to ischemic insult and AKI. The authors have provided the reasoning that blood product transfusion may trigger a systemic inflammatory response and that the resulting deterioration in hemodynamic parameters may cause AKI. This hypothesis needs further evidence as routine blood transfusions in other settings do not normally lead to AKI.

It is also noteworthy that Demiroz D et al. did not find pre operative bilirubin levels or postoperative clearance of jaundice as one of the predictors of AKI which have been reported previously.[4,5] In fact none of the clinical indicators of the severity of pre-op liver dysfunction had an independent association with AKI in the current study.[7] It is possible that children with significant pre-op liver dysfunction had co-existing renal dysfunction and were

excluded from the present study. Excluding such children may not be an appropriate decision for clinical research as children with pre-existing renal issues are more prone to AKI and should ideally be part of any research focusing on identifying and preventing risk factors of AKI. The overall in hospital mortality of the LT patient (26%) reported by Demiroz D et al. also seem higher than the previous reports. Others have reported mortality lower than 4% in their patients.[4,5] The authors do not offer any explanation for this observation and it is intriguing that the authors encountered much higher mortality in their children with significantly less occurrence of AKI. Did early post operative mortality mask the occurrence of AKI among those who expired early? Hence there are many unanswered questions in the data presented by Demiroz D et al. Being a large series involving 235 children, a relook at the data with better analysis can offer valuable insights. Moreover follow-up data to identify the occurrence of CKD will also be very useful for clinicians. Others have reported CKD in 28–86% of long-term survivors of pediatric liver transplantation.[3]

To summarize, the reported risk factors for AKI in liver transplant children seem to have the familiar mechanisms of ischemia and toxin-mediated injury predominantly. Since most of these modifiable risk factors appear to arise from the exact situations which the transplant team diligently tries to avoid, unique and easily implementable preventive strategies seem to be elusive. With the current knowledge, our best foot forward is to identify children at risk of AKI early for prognostication and possible intervention, if required. The fact that most of the children with AKI did not require renal replacement therapy (RRT) in most reported studies is reassuring, albeit the long-term risk of developing CKD does remain.

Orcid

Narayanan Parameswaran https://orcid.org/0000-0002-8297-5789

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