Statistical versus clinical significance

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Central Message

Allopurinol use decreases inflammatory markers; however, the clinical significance of its use remains to be explored.

See Article page 335.

Talwar and colleagues¹ performed a prospectively randomized study where they divided a cohort of 50 children with tetralogy of Fallot (TOF) into 2 equal groups (25 patients each) who received either 5 doses of oral allopurinol (10 mg/kg/dose) or placebo at 12 hours before surgery; before moving to the operating room; and then at 12, 24, and 36 hours after surgery. They found that the postoperative levels of interleukin 1- β , interleukin 6, malondialdehyde, and plasma troponin-I were all statistically higher in the placebo group, suggesting that the use of allopurinol, a xanthine oxidase inhibitor, is associated with diminished inflammatory response and decreased myocardial cell injury following cardiopulmonary bypass (CPB) and ischemic cardiac arrest during TOF repair. At the same time, the authors noted that allopurinol use was associated with lower inotropic score (median, 10 vs 15; $P = .02$), shorter mechanical ventilation (median, 7 vs 8 hours; $P = .01$), intensive care unit stay (median, 32 vs 48 hours; $P = .001$), and hospital stay (median, 5 vs 6 days; $P = .01$). The calculated cardiac index at 6 hours after surgery was higher in the allopurinol group, whereas the incidence of cardiac arrhythmias and the amount of pleural tube drainage were comparable. They concluded that the use of allopurinol might be associated with improved recovery and early outcomes following TOF repair.

The association between CPB and systemic inflammatory response is well established, although the full extent of this very complex process has not been entirely interpreted.²⁻⁴ Similarly, the relationship between the activation of various inflammatory cascades during CPB and postoperative myocardial and end organ dysfunction with subsequent postoperative morbidity and prolonged recovery is well demonstrated, especially in the small neonates undergoing complex cardiac reconstructions.²⁻⁴ Naturally, this undesirable affiliation has prompted many investigators to explore various methods to decrease the inflammatory response to CPB. Those methods included alterations of the CPB circuit (eg, using biocompatible coated surfaces and miniaturization of the circuit), blood-

conservation methods, ultrafiltration, and the use of multiple anti-inflammatory agents such as aprotinin, corticosteroids, and aspirin to list a few.^{5,6} Corticosteroids are the most commonly studied medications that have been used as prophylactic anti-inflammatory therapy in children undergoing CPB, although the type, timing, frequency, and dosage have widely varied among investigators.⁵⁻¹⁰ The results of corticosteroid use have been similarly diverse and whereas several studies showed reduction in inflammatory markers, the effects on postoperative hemodynamic parameters, recovery, and early clinical outcomes have not been consistent and in fact, a number of reports raised concern about the safety of corticosteroids and potential increased risk of infection, renal damage, and neurologic insult.⁵⁻¹⁰ Despite the large amount of research on the topic, the prophylactic preoperative and postoperative use of corticosteroids in congenital cardiac surgery remains debatable.

In this prospectively randomized study of the effect of allopurinol in modulating inflammatory response and myocardial dysfunction following CPB, the authors showed statistical differences in a number of the inflammatory markers and clinical parameters.¹ The implications of this study on clinical practice are questionable. As we have learned from the numerous corticosteroid studies, the differences of postoperative inflammatory markers do not always correlate with differences in clinical outcomes. Additionally, the study population is not necessarily one that continues to be highly problematic in the current era of advanced perioperative care; operative mortality is very rare in nonneonatal TOF repair and postoperative recovery

is commonly straightforward, aside from an occasional incidence of postoperative tachyarrhythmia.¹¹ Inotropic score is generally used to compare the amount of inotropic and vasoactive agents used following cardiac surgery. Nonetheless, the use of those agents is not necessarily always guided by patient need but rather by what a physician anticipates a patient will need. There are surely variations among physicians and certainly between institutions in the threshold to initiate, the type, and the amount of inotropes and vasoactive agents, and in the timing and rate of weaning of those medications following surgery. In most institutions, the inotropic score following an elective TOF repair rarely exceeds 10, which is similar to the score in patients who received allopurinol in the current study. Despite the statistical significance in inotropic score between the 2 study arms, it is difficult to demonstrate whether or not the amount and longevity of the use of those agents was dictated by the hemodynamic condition or clinical need of the patients. Additionally, whereas the duration of mechanical ventilation, intensive care unit stay, and hospital stays between the 2 groups of patients were all statistically lower in the allopurinol group (eg, a duration of ventilation 7 vs 8 hours), it remains questionable whether those are clinically significant, truly guided by patient needs and not influenced by logistic factors. For example, many programs implement a fast-track protocol following TOF repair with those patients extubated in the operating room, underscoring the physician factor that influences the recovery of those patients.¹² The 2 reasons that commonly require prolonged intensive care unit or hospital stays following TOF repair are arrhythmias and prolonged drainage from the chest drains, and those were both comparable between the 2 groups of patients.

Rather than dismiss the findings of this nice, prospectively randomized study,¹ we should consider where to proceed from here. Should we examine the effect of allopurinol on modifying the inflammatory response to CPB in vulnerable populations such as neonates undergoing complex cardiac procedures? Given the multitude of variables that influence the activation of those complex inflammatory cascades, would we be able to perform single-institution studies powered to demonstrate allopurinol's effect on inflammatory markers and more importantly clinical parameters? Given that allopurinol is a cheap medication, it is unlikely that the industry will invest in a multi-institutional effort to examine the role of this medication in this area. Should there be a multi-institutional effort to

examine this medication? How can we avoid the many hurdles that have complicated similar studies examining corticosteroids in the past? What do we know about the safety of allopurinol use in small children undergoing CPB? Most of what we know about the side effects of this medication comes from chronic use in adults with other medical conditions. Despite about 2 decades of investigation into the role of corticosteroids in children undergoing CPB, the issue remains debatable due to many of those limitations and it is likely that efforts examining the role of allopurinol in those patients will face the same limitations. Meanwhile, the statistical significance that has been demonstrated in this study might not be meaningful enough to influence a practical application.

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