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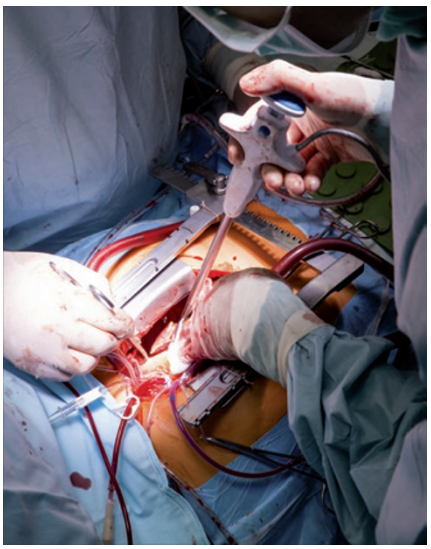
ACUTE KIDNEY INJURY

Fenoldopam infusion does not reduce the need for RRT in patients with AKI after cardiac surgery

The dopamine D1 receptor agonist fenoldopam mesylate does not prevent deterioration of renal function in patients with early acute kidney injury (AKI) after cardiac surgery, according to new findings from a randomized controlled trial (RCT) by Tiziana Bove and colleagues. These data are particularly disappointing because previous small RCTs and meta-analyses have suggested a nephroprotective effect of fenoldopam in critically ill patients with, or at risk of, AKI.

Although not approved by the FDA for renal indications, fenoldopam has been widely used off-label in the USA for nephroprotection in cardiac surgery and in other settings. "The pathophysiology and pharmacology of this drug is attractive—it dilates kidney and coronary arteries," explains Bove. A reduction in renal blood flow and activation of the sympathetic nervous system and renin–angiotensin system can occur as a result of decreased cardiac output during cardiac surgery. This mechanism, which leads to renal ischaemia—particularly in the medulla—is thought to have a major role in the development of postoperative AKI. As fenoldopam selectively binds dopamine D1 receptors, which are expressed in the medial layer of renal vessels, but does not have a high affinity for dopamine D2 receptors, the drug theoretically induces greater vasodilation in the renal medulla than in the cortex.

To test whether fenoldopam therapy can attenuate renal injury in patients with AKI after cardiac surgery, Bove and colleagues randomly assigned 667 patients who were admitted to cardiac intensive care units (ICUs) in Italy with early postoperative AKI (defined as a ≥50% increase in serum creatinine level from baseline or oliguria for ≥6 h) to receive continuous infusion of fenoldopam ($n = 338$) or placebo ($n = 329$) for up to 4 days. All participants underwent follow-up monitoring 30 days after surgery.



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In their prespecified interim analysis, the researchers found no significant difference in the primary end point of rate of renal replacement therapy (RRT) administration (that is, continuous venovenous haemofiltration or haemodialysis) in the fenoldopam (20%) and placebo groups (18%, $P = 0.47$). Moreover, serum creatinine levels were similar in the two groups throughout the study period.

The secondary end points of ICU mortality, 30-day mortality, length of ICU and hospital stay, time receiving mechanical ventilation, peak serum creatinine level and incidence of AKI (according to RIFLE criteria injury and failure definitions) also did not differ significantly between the study groups. However, a significant difference was reported in the secondary end point of hypotension during study drug infusion, which occurred in 26% of patients in the fenoldopam group compared with only 15% of patients in the placebo group ($P = 0.001$). Following this interim analysis, the study was stopped on the recommendation of an independent safety committee because of futility of the intervention.

The researchers suggest that the well-known limitations of small single centre RCTs and meta-analyses might explain why the findings of their study—the largest multicentre RCT of fenoldopam in the setting of cardiac surgery conducted to date—might differ from those of previous studies. As their trial protocol was simple and, with the exception of study drug infusion, routine practice was maintained throughout, they suggest that their results are likely to be highly reproducible. They conclude that "given the cost of fenoldopam, the lack of effectiveness, and the increased incidence of hypotension, the use of this agent for renal protection in [patients with AKI after cardiac surgery] is not justified," and hypothesize that the drug is also not likely to be effective for the prevention of AKI in other settings.

Bove and colleagues are now focusing their research efforts on other areas. "We are already using the network of 19 centres that participated in this trial to test other drugs, techniques and strategies and improve patient outcomes," says senior investigator Giovanni Landoni. "We have also recruited 150 hospitals from 50 countries to participate in our next trial, which will compare two different anesthesiological techniques in terms of 1-year survival after cardiac surgery." He emphasizes that investigator-driven trials are performed in the interest of patients, and that all participants benefit when off-label drug uses and standard techniques and/or strategies are compared. "Patients, politicians and bureaucrats should understand that these studies must be supported and all costs and impediments removed."

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