Neuroanesthesia and Intensive Care

Best evidence in anesthetic practice

Prevention: dopamine does not prevent death, acute renal failure, or need for dialysis

Article appraised

Kellum JA, Decker JM. Use of dopamine in acute renal failure: a meta-analysis. *Crit Care Med* 2001; 29: 1526–31.

Structured abstract

Question: Does low-dose ($< 5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) dopamine prevent death, acute renal failure (ARF), or hemodialysis requirements in critically ill patients?

Data sources: Studies were identified by MEDLINE (1966–1999) search for articles on kidney (drug effects) and dopamine, limited to clinical trials and systematic reviews. Citation review of original reports and reviews was also performed.

Study selection: Studies were selected if they were studied human subjects, used low-dose ($< 5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) dopamine to prevent or treat ARF, and reported primary data on death, development or worsening of ARF, or hemodialysis requirement. The diagnosis of ARF required biochemical criteria $\pm$ oliguria; indication for hemodialysis required clinical criteria or use of any renal support at least once for a given patient. Biochemical and clinical criteria were not standardized.

Data extraction: Data were extracted on trial design, patient characteristics, mortality rates, inci-

dence and severity of ARF, and use of hemodialysis. Meta-analysis was restricted to data from randomized clinical trials.

Main results: Seventeen trials with a total of 854 patients met the inclusion criteria. Low-dose dopamine did not change the frequency of death, onset of ARF, or hemodialysis requirements (Table). Subgroup analyses did not show any statistical differences in outcomes in patients without exposure to radiocontrast dye or in patients with cardiac disease.

Conclusions: Low-dose dopamine does not increase or decrease death, onset of ARF, or hemodialysis requirements.

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Correspondence: Dr. John A. Kellum, University of Pittsburgh Medical Center, Division of Critical Care Medicine, 200 Lothrop Street, Pittsburgh, PA 15213-2582, USA. E-mail: kellumja@anes.upmc

Commentary by D. Bracco

Since the original work by McDonald in 1964, showing that low doses of dopamine increase diuresis and natriuresis in healthy volunteers, administration of dopamine in patients with or at risk of acute renal failure (ARF) has become a worldwide practice.

TABLE Effect of low-dose dopamine on mortality, onset of acute renal failure, and hemodialysis requirement

Outcome	Events		Risk ratio* (95% CI)	P-value
	Low-dose dopamine	No low-dose dopamine		
Death	12 / 258	14 / 250	0.86 (0.44; 1.66)	Not significant
Onset of acute renal failure	38 / 253	59 / 270	0.72 (0.51; 1.03)	Not significant
Hemodialysis requirement	37 / 298	46 / 309	0.87 (0.62; 1.21)	Not significant

* Risk ratio less than 1 favours the dopamine group; risk ratio greater than 1 favours the no dopamine group. Values have been recalculated.

FIGURE Action of dopamine in the kidney

Physiologic basis of action of dopamine on the kidneys

At low concentrations, dopamine acts on DA adrenergic receptors in the kidney's vascular bed and tubule. Activation of these receptors leads to renal vasodilation and inhibition of proximal sodium reabsorption. The increased renal blood flow and glomerular filtration rate results in diuresis and natriuresis. However, this observation has not been demonstrated clearly in critically ill patients.

The increased sodium load delivered in the distal tubule must be reabsorbed. Sodium reabsorption is energy consuming. Dopamine increases diuresis and natriuresis at the expense of increased oxygen demand (Figure). ATP depletion in the kidney during ARF has been demonstrated by magnetic resonance imaging.¹

Why dopamine doesn't work in critically ill patients

Renal failure is a very common complication of shock states and contributes significantly to mortality and length of stay. In most cases, renal failure in the critically ill is secondary to decreased oxygen supply to the kidney. Renal failure in these patients encompasses a broad spectrum of cellular dysfunction ranging from transient functional impairment to complete tubular necrosis.

In a hypoxic kidney, administration of a drug that potentially increases oxygen demand represents a risk. If renal vasodilation is insufficient to overcome the increased oxygen demand, dopamine could worsen hypoxia and could lead subsequently to renal failure.

Low-dose dopamine ($0.5\text{--}2\text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) results in plasma levels 100 times greater than normal physiological levels. Plasma dopamine clearance is reduced in critically ill patients. The pharmacokinetics and pharmacodynamics of dopamine in the critically ill are difficult to predict. An indirect effect on cardiac output

and blood pressure must be taken into account. Improvements in systemic hemodynamics may affect local and regional blood flow. The administration of low-dose dopamine is not harmless: it may increase cardiac output and oxygen demand and expose the patient to an increased risk of arrhythmia and myocardial ischemia. It interferes with the endocrine system (decreased prolactin, growth hormone, and thyrotropin), electrolyte balance (hypokalemia and hypophosphatemia), metabolism (negative nitrogen balance), and the immunological system (decreased T-cell function).

Kellum and Decker's meta-analysis, which includes 17 studies on 854 patients, shows no improvement in extracorporeal support or mortality. These findings have been confirmed by two recent studies^{2,3} showing no difference in the evolution of renal failure, the need for extracorporeal support, and mortality. The Australasian study had detailed end points in which no beneficial effect of dopamine was demonstrated.²

The time has come to examine the evidence. There are no data from prospective, well-controlled, randomized clinical trials that support the use of dopamine in critically ill patients with ARF or at risk of ARF. "Physiological" data in volunteers with a large oxygen balance reserve cannot be extrapolated to critically ill patients where impaired renal oxygen balance is the fundamental mechanism leading to ARF.

David Bracco MD
Lausanne, Switzerland

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Commentary by J. L. Parlow

Kellum and Decker have set out to definitively answer the question of whether dopamine has renal protective properties in critically ill patients.¹ This paper is of interest to both intensivists and operative anesthesiologists, in that the studies analyzed include both critical care and high risk operative patients.

In the design of this study, the authors have satisfied most of the desirable criteria for a meta-analysis.² MED-

LINE and manual searching was done of 33 years of literature. Although it is arguable whether or not elective vascular and cardiac surgical patients fall into the category of "critically ill" patients, the included population encompasses a wide range of patients who are at increased risk of acute renal failure (ARF) and who commonly receive prophylactic dopamine infusion. The endpoints studied are clear and important, including death, requirement for hemodialysis, and development or worsening of ARF. An inherent limitation of meta-analysis is that the operational definitions of ARF and need for dialysis differed in the various trials – it seems only death could be defined to all investigators' satisfaction! Furthermore, sufficient power was attained for only two of the primary outcomes: development of ARF and need for hemodialysis.

The authors report that, despite traditional thinking, dopamine has no effect on the development of ARF. In their discussion, the authors boldly state that dopamine should not be used for the prevention or treatment of ARF and provide a rationale for this conclusion. Although dopamine increases renal blood flow, decreased renal blood flow does not necessarily result in ischemic ARF and increased renal blood flow does not necessarily prevent this injury. In fact, the authors refer to previous work suggesting that dopamine may worsen renal injury in certain situations, despite increasing renal blood flow, and that anti-dopaminergic agents are not associated with ARF although they block the renal vascular effects of dopamine.

From the clinical perspective, the mechanisms involved in perioperative ARF may be distinct from those involved in nonoperative critically ill patients. Of the 58 studies reviewed, 20 involved surgical patients; only nine of these reported outcomes studied in this meta-analysis. Patients undergoing vascular and cardiac surgery (totalling 256) comprised only four of the studies analyzed. Thus, there was insufficient power to analyze these patients as a subgroup. When one examines the results of the perioperative trials, there was not even a trend to suggest a beneficial effect with dopamine.

What can we conclude? Many etiological factors involved in perioperative ARF may be specific to the perioperative setting, including particular nephrotoxic agents, hypotension from hypovolemia, cardiopulmonary bypass, and abrupt hypoperfusion from aortic cross clamping;³ however, despite the low numbers of perioperative patients examined in this study, the authors provide as much physiological rationale against the use of dopamine as supporting it. Thus, based on the *existing* evidence, one can conclude that perioperative prophylactic dopamine is not better than

placebo and that even the theoretical benefit of dopamine is uncertain. The authors conclude their paper with the recommendation that further study of the effects of dopamine should be undertaken only as large, well-powered randomized clinical trials. Given that perioperative ARF remains a common and ominous complication, further large-scale investigation into effective means of prevention is warranted.

Joel L. Parlow MD FRCPC MSc
Kingston, Ontario

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