Management options

Can the use of low-dose dopamine for treatment of acute renal failure be justified?

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Summary

The use of dopamine for the prevention and treatment of acute renal failure is widespread. Its use is based on physiology suggesting selective renal vasodilation when it is infused at low dose. This article reviews the available data on the clinical use of dopamine. When used to prevent acute renal failure in high-risk treatments there is no evidence of benefit of dopamine but, given the low incidence of significant renal failure, the studies are underpowered. In treatment of acute renal failure, the quality of the data is poor. Only in one small randomised trial of moderate acute renal failure in patients with malaria was a clinically significant benefit of dopamine shown. The rest of the data, in the form of case series, showed either no benefit of dopamine or small benefits of little clinical significance. Again, these studies are of insufficient power for conclusions to be drawn as to the overall benefits and risks. We conclude that benefits of dopamine use cannot be ruled out by currently available data but its use cannot be advised until trials examining clinically important endpoints in large numbers of patients have been performed.

Keywords: dopamine; renal failure

The use of dopamine for prevention and treatment of acute renal failure is based on its ability to increase renal blood flow in animals¹ and in normal human subjects.^{2,3} Early case reports⁴ appeared to confirm the benefit of dopamine which has become widely used for the treatment of patients with acute renal failure. However, more recently the benefits of dopamine have been questioned,⁵ and more attention given to its risks.⁶ Denton *et al*⁷ concluded that renal dose dopamine “should not be used for its selective renal vasodilatory actions in patients with acute renal failure until its efficacy is established conclusively.” We have reviewed the published literature using a Medline search and tracing back references from recent publications to determine whether the current use of dopamine for management of acute renal failure can be justified by the currently available evidence.

The normal physiology of dopamine,

The effects of dopamine infusion are complex as it acts on a number of different receptors which have opposing actions.³ Dopamine can stimulate β_1 -adrenoreceptors and increase cardiac index.⁸ At high dose, dopamine interacts with peripheral α_1 -adrenoreceptors to bring about systemic vasoconstriction.⁹ In addition, there are two major subgroups of dopamine receptors. DA_1 Receptors have been demonstrated on renal, mesenteric, coronary and cerebral arteries,¹⁰ while DA_2 receptors are located in autonomic ganglia and sympathetic nerve endings where they inhibit noradrenaline release¹¹; they also inhibit aldosterone production in the adrenal gland.¹⁰ Given the complexity of dopamine's actions it is unsurprising that there is overlap of the doses at which its various effects are seen and no dose is specifically renal in action.¹²

In normal animals, dopamine infusion increases renal blood flow, although this is dose-dependent and the dose range varies between species.¹³ In man, low-dose dopamine (0.5–3.0 $\mu\text{g/kg/min}$) increases renal blood flow, measured using *p*-aminohippuric acid clearance,² by stimulation of DA_1 receptors.¹⁴ In normal dogs low-dose dopamine results in an increase in glomerular filtration rate (GFR).¹⁰ Evidence of a change in GFR in man is conflicting. McDonald *et al*² found an increase in inulin clearance from 109 to 126 ml/min with dopamine infused up to 7.1 $\mu\text{g/kg/min}$ in normal humans whilst Ramdohr *et al*¹⁵ found no significant change in GFR.

Dopamine causes diuresis and natriuresis independent of any effect on renal blood flow by acting on proximal tubular cells. It inhibits proximal tubular $\text{Na}^+\text{K}^+\text{ATPase}$ by a mechanism which, in the rat, requires stimulation of both DA_1 and DA_2 receptors.¹⁶ Through an effect on DA_1 receptors, dopamine also modulates the proximal tubular Na^+/H^+ exchanger, decreasing V_{max} with no effect on K_m .¹⁷

Rationale for use of dopamine in acute renal failure

Acute renal failure frequently follows renal hypoperfusion, often in combination with other toxic insults such as sepsis, rhabdomyolysis, or exogenous agents such as drugs or radiocontrast medium.¹⁸ Mild circulatory failure can be compensated for by local mechanisms in the kidney which preserve renal blood flow and GFR. Moderate renal hypoperfusion results in a loss of GFR and prerenal acute renal failure which is reversible rapidly if the circulation is adequately restored. Severe hypoperfusion results in renal ischaemia which, if not rapidly reversed, often causes persistent renal failure.

This persistent acute renal failure is often associated with histological evidence of acute tubular necrosis (ATN). However, histological ATN is not invariable, leading to the suggestion that haemodynamic factors are crucial in the develop-

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ment and maintenance of acute renal failure.¹⁹ GFR is highly dependent upon glomerular perfusion which is affected by a large number of vasoactive substances within the kidney.¹⁸ Dopamine could alter renal haemodynamics and thus maintain glomerular perfusion. Increased renal perfusion might also prevent tubular ischaemia and hence prevent ATN. Once ATN is established there may be benefit from a dopamine-induced natriuresis and diuresis in washing out obstructing tubular casts which could be involved in preventing early recovery of renal function.⁷ Diuresis may also simplify fluid management. Even in acute renal failure secondary to nephrotoxins intrarenal vasoconstriction may be important and its reversal by dopamine of use therapeutically.⁷ Since renal vasoconstriction and hypoperfusion are most likely during the earliest phases of development of acute renal failure, the use of dopamine to prevent renal failure in patients undergoing high risk procedures is an attractive proposition.

Effect of dopamine in animal models of acute renal failure

The effect of dopamine on the development of acute renal failure has been investigated in a variety of animal models. Most widely studied is the ischaemic model brought about by clamping of the renal arteries. Iania *et al*²⁰ infused dopamine 6 µg/kg/min from 15 minutes prior to until 30 minutes after clamping the renal artery for 70 minutes in rats which had undergone contralateral nephrectomy. Rats receiving dopamine had lower serum creatinine, serum urea and higher inulin clearance 24 hours later. These investigators concluded that the benefit seen at 24 hours was due to effects immediately after release of the clamp.²¹ Pollock and Oppenorth²² investigated the effect of dopamine in rats that had been subjected to bilateral renal artery clamping for 30 minutes. Dopamine was administered at 10 µg/kg/min for 1 hour following removal of the clamps. Inulin clearance 1–2 hours post clamping was no different in the dopamine group compared to controls. There was no difference in serum creatinine in the dopamine group up to day 4 and histology on day 4 was the same in controls and dopamine-treated animals. Similar experiments have been performed in dogs in which dopamine infused intravenously at 3 µg/kg/min for 60 minutes following removal of renal artery clamps produced no improvement in GFR.²³

Acute renal failure can also be caused in animal models by glycerol-induced rhabdomyolysis,²⁴ nephrotoxic agents such as uranyl nitrate,²⁵ septic shock,²⁶ or haemorrhage.²⁷ In glycerol-treated rats Drieman *et al*²⁴ did not demonstrate any change in renal blood flow using low-dose dopamine (1.6 µg/kg/min) whilst high-dose dopamine (16 µg/kg/min) resulted in increased mortality. However, Gómez-Garre *et al*²⁸ in the same model showed maintenance of normal urine output, less decline in creatinine clearance and improved survival at day 3 in animals treated with dopamine (100 µg/h ≈ 6.7 µg/kg/min).

There have also been variable results of the use of dopamine in uranyl-nitrate-induced acute renal failure. In a short-term study the combination of dopamine (3 µg/kg/min) and frusemide was protective against an early fall in creatinine clearance in dogs when started 15 minutes after injection of uranyl nitrate.²⁹ In rabbits, dopamine (5 µg/kg/min) started 24 hours after injection of uranyl nitrate produced no benefit.³⁰

In a model of septicaemia, a modest reduction of GFR can be produced by infusing rats with *Escherichia coli*. Dopamine (2.5 µg/kg/min) in this model did not significantly improve GFR.²⁶ In dogs, haemorrhaged to a systolic blood pressure of 70 mmHg, dopamine (6 µg/kg/min) improved renal cortical blood flow but no data were presented on renal excretory function.²⁷ Finally the effect of dopamine on renal blood flow has been investigated in a model of obstructive jaundice in the baboon.³¹ Before bile duct ligation dopamine increased renal blood flow at very low doses (0.0005–0.05 µg/kg/min) but decreased renal blood flow at doses which would be considered renal-protective in man (0.5–5 µg/kg/min). After bile duct ligation, far from increasing renal blood flow, the increased blood flow seen with low doses in normal animals was largely abolished. There was no measurement of renal excretory function in this study.

Dopamine has been used in different models, in different species and using different doses given at different times. No consistent positive or negative responses have been reported. It is not possible to come to a conclusion from animal studies as to the likely effect of dopamine on acute renal failure in man.

Use of dopamine as prophylaxis in high-risk procedures

It seems logical to postulate that dopamine is most likely to be effective if used at the time of onset of the insult resulting in acute renal failure. Dopamine might therefore be used prophylactically to prevent acute renal failure under circumstances known to be of high risk. Studies of the use of dopamine in

Table 1 Studies investigating the use of dopamine in prophylaxis of high-risk procedures

Procedure	Studies in which dopamine was beneficial		Studies in which no effect of dopamine was demonstrated	
	Ref	No of patients	Ref	No of patients
Vascular surgery (abdominal aortic aneurysm/coronary artery bypass grafting)			32	37
			33	27
			34	52
Liver surgery	35	34 (less oliguria, no difference in dialysis requirement)	36	48
			37	23
Intravenous contrast media	38	24 (transient reduction in renal function in controls avoided in DA treated)	39	30
Renal transplantation			40	60
			41	167
			42	60
			43	40

prophylaxis suffer from small numbers, lack of controls and the use of different infusion regimes. Table 1 gives references to studies in this area, divided into those showing a benefit of dopamine and those showing no effect.

In a prospective randomised controlled trial in 37 patients undergoing elective abdominal aortic aneurysm surgery, Baldwin *et al*³² showed no benefit of using dopamine post surgery. Similarly, no benefit of dopamine use has been demonstrated in patients undergoing elective infrarenal aortic cross-clamping³³ or elective coronary surgery.³⁴

In liver transplantation, Polson *et al* reported an uncontrolled retrospective analysis of 36 liver transplants³⁵ in which 21 had received prophylactic dopamine infusion (2 µg/kg/min). There was a higher rate of oliguria in the group which did not receive dopamine but no significant difference in the rate of dialysis requirement. Swygert *et al* performed a prospective randomised controlled study of dopamine (3 µg/kg/min) in 48 patients undergoing liver transplantation.³⁶ There was no difference in serum creatinine after 7 days or GFR (iothalamate clearance) after 1 month. There was no difference between the groups in incidence of dialysis requiring acute renal failure (4.0% placebo group *vs* 4.5% dopamine group) and no difference in mortality. Similarly, in surgery for obstructive jaundice, Parks *et al* did not demonstrate a benefit of dopamine infusion, perhaps because of a lack of acute renal failure in the control group.³⁷

Intravenous contrast used for angiography can cause acute deterioration in renal function. Hall *et al*³⁸ in a prospective study of 24 patients (initial creatinine >2.0 mg/dl) found that dopamine (3 µg/kg/min) prevented the deterioration in renal function seen in the control group. However, only one patient in the study required dialysis, and no effect was observed in patients whose pre-procedure creatinine was less than 2.0 mg/dl. A benefit of dopamine in this study was shown in subjects with pre-existing renal disease, although ter Wee *et al* showed that the effect of dopamine on effective renal plasma flow and glomerular filtration rate was lost once GFR fell below 50 ml/min/1.73 m².⁴⁴ Weisberg *et al* investigated 30 patients with chronic renal impairment undergoing angiography. In a randomised controlled trial using a short infusion (15 minute pre- and 2 hours post-procedure) they noted a high incidence of deterioration in renal function (defined by 25% increase in serum creatinine) but no benefit of dopamine.³⁹

Renal transplantation is often complicated by initial acute renal failure attributed to acute tubular necrosis. Low-dose dopamine increases effective renal plasma flow and GFR in normal individuals after taking cyclosporine A⁴⁵ and in stable renal transplant recipients.⁴⁶ However, none of the studies published to date has demonstrated a benefit of using dopamine immediately post-transplantation in terms of length of primary non-function, need for dialysis, or ultimate kidney function.⁴⁰⁻⁴³

As indicated in table 1, few of the published studies have shown a significant benefit of dopamine use. Although used in procedures considered to be relatively high risk, the incidence of acute renal failure is nevertheless small and none of the published studies are therefore of sufficient power to detect a benefit. It would be necessary to treat a large number of patients never destined to suffer renal failure in order to prevent a single episode. Given the side-effects of dopamine described below, the use of dopamine as prophylaxis is not currently justified, except possibly as part of adequately powered randomised trials.

Use of dopamine in acute renal failure

In 1970 Talley *et al*⁴⁷ reported an uncontrolled series of five patients with acute oliguric renal failure in whom a combination of dopamine (4 µg/kg/min) and

Table 2 Studies of the use of dopamine (DA) in patients with acute renal failure in which there had been an assessment of renal excretory function and there were sufficient controls to enable interpretation. ARF=acute renal failure, ICU=intensive care unit

Ref	No of patients	Setting	Controls	Added diuretic	Dopamine dose	Effect
48	15	Cardiac surgery	Assesment before and during DA in individual patients	No	100 µg/min	Creatinine clearance increased from 70±10 to 115±13 ml/min with DA
50	11	ARF in ICU	Assessment before and during DA in individual patients	Prior treatment with frusemide	1 µg/kg/min	No difference in serum creatinine with DA
51	52	ARF in ICU	Assesment before and during DA in individual patients	Frusemide	1.5–2.5 µg/kg/min	Creatinine clearance increased by mean of 3.8±1.0 ml/min with DA
55	256	ARF of ischaemic or toxic origin	Non-randomised controls	Physician discretion	<3 µg/kg/min or >3 µg/kg/min	No benefit of DA at either dose in preventing death or dialysis
56	23	ARF due to malaria	Randomised controlled	Frusemide	1 µg/kg/min	Renal function stabilised in DA group if creatinine <398 µmol/l

diuretic treatment produced apparent improvement in renal function. In the same year Barnardo *et al*⁴⁷ showed that dopamine increased inulin clearance in 10 patients with liver cirrhosis and renal impairment. The greatest effect of dopamine was in those with the best initial renal function.

Over the following three decades dopamine has become widely used as a treatment for acute renal failure but data to support its use are sparse. Most evidence is in the form of uncontrolled case series in which it is a consistent finding that dopamine infusion, with or without diuretics, increases urine output and fractional excretion of sodium.^{48–54} Unfortunately, urine output is a notoriously poor indicator of GFR. Few studies have investigated effects of dopamine on excretory renal function, those which have with sufficient controls to make them interpretable are shown in table 2. Parker *et al*⁵¹ found an increased creatinine clearance in 52 oliguric patients on administration of dopamine. However the increase of 3.8 ml/min/1.73 m² is of doubtful clinical significance. Davis *et al*⁴⁸ found an increase in creatinine clearance in nine oliguric patients treated with dopamine following cardiopulmonary bypass; the creatinine clearance returned to baseline on stopping dopamine. In these patients the baseline GFR was 70±9 ml/min and any increase was therefore unlikely to be of clinical relevance.

Lumlertgul *et al*,⁵⁶ in a small randomised controlled trial, treated acute renal failure caused by malaria with dopamine and frusemide. This combination, but not frusemide alone, prevented further significant increase in serum creatinine in four patients with moderate renal failure (creatinine 257–389 µmol/l). Three out of four patients in the control group required dialysis compared with none of those treated with dopamine. The time to recovery of renal function was significantly shorter in the dopamine group than in the control or frusemide alone groups. Amongst five patients with severe renal failure (creatinine > 600 µmol/l) at presentation there was no benefit of dopamine over controls.

Chertow *et al*⁵⁵ recently published data on the use of dopamine in a relatively large number of patients with acute renal failure. The data were derived from a secondary analysis of the control group in a study primarily investigating the use of atrial natriuretic peptide. The use of dopamine within the study was left to the discretion of the participating physicians and was not randomised. In total, 79 patients were not treated with dopamine, 86 were treated with 'low dose' dopamine (3 µg/kg/min) and 91 with 'high dose' dopamine (>3 µg/kg/min). The relative risk of death or dialysis, after adjusting for the fact that patients treated with high-dose dopamine tended to have more severe illness, was 0.95 (confidence interval (CI) 0.58–1.58) in the low-dose dopamine group and 1.02 (CI 0.63–1.69) in the high-dose dopamine group. Thus, no significant benefit of dopamine treatment was demonstrated.

The potential harmful effects of dopamine

Dopamine has a number of known side-effects even at low dose (table 3). These include tachyarrhythmias and increased left and right ventricular afterload,³ depressed respiratory drive⁵⁷ and increased intrapulmonary shunting.⁵ Dopamine, if given via peripheral vascular access, can extravasate and cause local ischaemia and necrosis.⁵⁸ If given through a central line, the risks of line insertion are added. There is also the risk of provoking diuresis in an already volume-depleted patient.⁶ Dopamine has a number of endocrine effects of uncertain significance⁶² and may alter immune responses by affecting T cell proliferation.⁵⁹

Gut ischaemia is thought to be important in the development of multisystem organ failure in critically ill patients.⁶³ Dopamine as a mesenteric vasodilator³ might be expected to improve gut ischaemia. In 25 critically ill patients treated with dopamine Maynard *et al* did not find the expected improvement in

Table 3 Side-effects of dopamine use

Harmful effects of dopamine	Ref
Tachyarrhythmias	3
Increased left and right ventricular afterload	3
Depressed respiratory drive	57
Interpulmonary shunting	5
Extravasation causing local necrosis	58
Risks of central line insertion	
Over diuresis in volume depletion	6
Altered immune responses	59
Possible gut ischaemia	60, 61

splanchnic perfusion.⁶⁰ It is of concern that in a porcine model of haemorrhagic shock there is evidence that low-dose dopamine in fact shunts blood away from the gut mucosa and increases gut ischaemia.⁶¹

The effects of dopamine vary considerably with the dose. Based on physiology in healthy subjects³ a low dose of dopamine is used to treat acute renal failure. Critically ill patients have reduced dopamine clearance which is also very variable compared to controls and consequently they have higher plasma levels of dopamine.^{64 65} Any dopamine dose could therefore have beta- and alpha-agonist effects, as well as dopamine receptor agonist effects, and it is not correct to assume that low-dose dopamine acts specifically on renal vasculature. Tolerance to the vasodilatory effects of dopamine has been demonstrated within 2 to 3 days of starting treatment, thus adding further to the variability of response.⁶⁶

Conclusion

Dopamine use in acute renal failure is widespread, in spite of the publication of several reviews advising caution.^{5-7 67 68} The quality of the currently available evidence is not sufficient to allow the use of statistical techniques such as meta-analysis to improve our understanding of the relative benefits and risks of dopamine use. There is no convincing evidence to support its use as a prophylactic agent and there are insufficient data to confirm or refute the hypothesis that dopamine is of use as a treatment of acute renal failure. The evidence that dopamine treatment has significant side-effects means that it is no longer advisable to use it on the basis that it may do good whilst causing no harm. It remains possible that the benefits of dopamine treatment outweigh the risks but until this is properly studied in a large, randomised, controlled trial looking at end points such as mortality, need for dialysis or length of hospital and intensive care stay, it should only be used with caution.

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