The Controversy of Renal Dose Dopamine Administration in the Treatment of Acute Renal Failure

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ABSTRACT

Administration of a renal dose of dopamine in acute renal failure still attracts a lot of controversy, since there has not been a study that found a significant protective effect on the kidneys.

Nevertheless, according to its ability to increase renal blood flow in laboratory animals and normal subjects, several parties still maintain its use, even though the required dose is very much individualized.

The side effect of dopamine, such as tachycardia, arrhythmia, miocardiac ischemia, and intestinal ischemia due to precapilary vasoconstriction causing bacterial translocation from the intestinal lumen to the systemic bloodstream, even though relatively rare, should receive adequate attention.

Key words: *Renal dose dopamine, Acute renal failure*

INTRODUCTION

Dopamine is used for the prevention and treatment of acute renal failure based on its ability to increase renal blood flow in laboratory animals and normal subjects. Initial studies demonstrated greater benefits of dopamine use for the treatment of this condition. For example, low doses of dopamine are used in the intensive care unit to reduce renal problems.[1,2,3,4]

Lately, there has been a lot of argument among experts on the efficacy of this form of treatment, since there is inadequate data for the consideration of its use.[1,3]

Even though the concept of renal dose dopamine for the prevention of acute renal failure is still controversial, Denton et al in the Kidney International Journal concluded that renal dose dopamine can increase urine production and creatinine clearance in patients with acute renal failure and olyguria.[5]

In contrary to Denton et al, a randomized study on patients with pre-acute renal failure, Bellomo et al were not able to demonstrate the benefits of administration of renal dose dopamine for protection. Thus, we need to re-think whether the use of dopamine as a vassopressor agent and inotropic drug in patients with septic shock is still rational.[6]

THE NORMAL PHYSIOLOGY OF DOPAMINE

The structure of dopamine can be found in Figure 1.

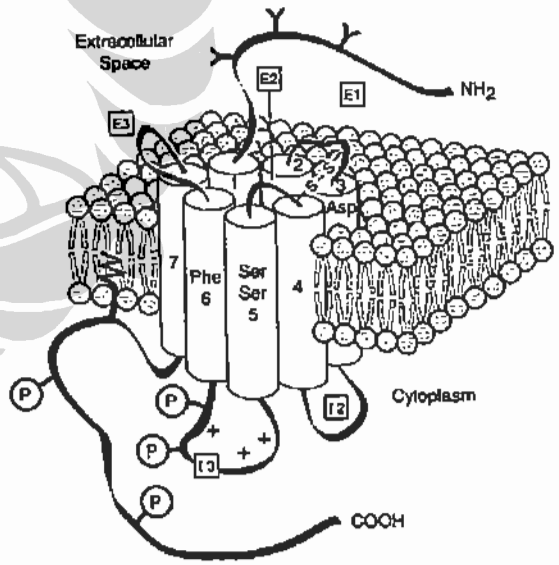

Figure 1. Dopamine Structure (quoted from reference no.8)

Dopamine is a catecholamine neurotransmitter in the mammal brain, which functions to control various functions, including locomotor, cognitive, and emotional activities, endocrine regulation, and dietary intake. Catecholamine also plays a role in the peripheral nerves as cardiovascular function modulators, catecholamine release, hormonal secretion, vascular tone, renal function, and gastrointestinal motility.[7,8]

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The biological effect of dopamine occurs through 5 genetically distinct receptors, known as D_1, D_2, D_3, D_4 and D_5.[9] Based on the similarity in protein structure and the stimulation-inhibition of adenyl-cyclase, there are 2 main groups of dopamine receptors, D_1-like or D1 (D_1 and D_5) receptors, and D_2-like or D2 (D_2, D_3 and D_4) receptors.[8,9] This can be seen in Table 1.

From pharmacological studies, we know that D1 receptors are found in the kidneys, mesenterium, coronary artery, and cerebral artery, while D2 receptors are found in the autonomic ganglion in the sympathetic nerve end, whose activity inhibits noradrenaline release and inhibits aldosteron production in the adrenal gland.

Dopamine is synthesized from L-Dopa, which circulates in the bloodstream through L-amino acid decarboxylase in the proximal tubules. There is also renal enervation containing dopamine, even though the mechanism of its action is still unclear.[7]

The effect of dopamine administration is very complex, in line with its action on a number of receptors distributed in the central as well as peripheral nervous system, with each different functions.[7,8]

Dopamine is a natriuretic hormone that functions to increase sodium excretion by reducing sodium reabsorption in the proximal tubules by the following mechanisms of action:

1. Stimulate the formation of cyclic AMPs, to reduce Na-H pump activity that plays a role in the entrance of filtrated sodium into the cell on the membrane lumen.
2. Inhibiting the action of Na-K-ATPase pump on the basolateral membrane. Under normal conditions, cellular sodium is transported into the peritubular interstitial tissue and then to the capillaries around the tubules.

Schematically, the mechanism of action of dopamine can be seen in Figure 2.

At high doses, dopamine interacts with alpha adrenergic receptors of peripheral blood vessels to cause vasoconstriction.[8]

Because the effect of dopamine stimulation is very complex, different doses of dopamine causes different effects.

In normal laboratory animals, dopamine administration increases renal blood flow, even though this depends on the dose and doses variation in each individual.[1,2,5]

In humans, low doses of dopamine (0,5-3 mg/kg bodyweight/minute) increases renal blood flow by dilating the interlobulary arteries as well as the afferent and efferent arterioles, calculated based on the PAH (para amino hippuric) acid clearance.[7,8,9]

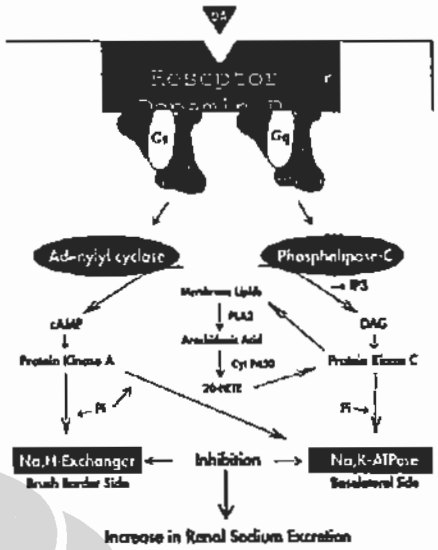

Figure 2. The Mechanism of Action of Dopamine (quoted from reference no.8)

Table 1. Peripheral Dopamine Receptors (quoted from reference no.8)

Receptor Type	Agonistic Substance	Site of action	Effect
D1 like	Dopamine	Blood vessels	Vasodilatation
	Fenoldopam	Renal tubules	Natriuresis, Diuresis
	Dopexamine, Ibopamine	Jukstaglomerular cells	Rennin release
D2 like	Dopamine*	Postganglionic sympathetic nerve	Vasodilatation, bradycardia
	Quinpirole	Sympathetic ganglion	Transmission Inhibition
	Bromokriptin	Glomerular zone cells	Inhibition of aldosteron Release
	Dopexamine Ibopamine	Renal tubules	?

* The dose required to activiate D2-like receptors is at least twice the dose needed to activate D1- like receptors.

In laboratory animals, low dose dopamine infusion causes an increase in glomerular filtration rate (GFR). However, evidence on this effect is still under debate. McDonald et al found an increased inulin secretion from 109 to 126 ml/minute with a dopamine infusion up to a dose of 7,1 mg/kg Bodyweight/minute in normal subjects. Ramdohr et al found a different result, where there was no significant change in GFR.[10,11]

Dopamine causes diuresis and natriuresis through its action at the proximal tubule by inhibiting the Na^+K^+ATP-ase pump activity, which in laboratory rats require stimulation of both D1 and D2 receptors. Through its action on D1 receptors, it causes the exchange of Na^+ and H^+ ions in the proximal tubules.[7,8,9,10]

CLINICAL USE

Based on this mechanism, dopamine is commonly used in small doses (0.5–3 mg/kg Bodyweight/minute) to increase urine production and maintain renal function during oliguria in patients with acute tubular necrosis (ATN).[7]

The Rationale for Using Dopamine in Acute Renal Failure

Acute renal failure followed by renal hypoperfusion often occurs during sepsis, rhabdomyolysis, or due to drugs or contrast media. Mild circulatory failure is compensated through a local mechanism by maintaining the renal blood flow and GFR. Moderate hypoperfusion causes a reduction in GFR and a pre-renal acute renal failure that is quickly reversed as the systemic circulation returns to normal. Severe hypoperfusion causes renal ischemia, which if remains untreated, may cause permanent renal failure.[6,10,11,12,14]

Permanent acute renal failure is commonly associated with the histological change of acute tubular necrosis. The pathological findings of acute tubular necrosis makes the haemodynamic factor the main focus in the development on the knowledge and treatment of renal failure. GFR completely depends on glomerular perfusion, which influences most of the renal vasoactive substance. Dopamine can change the renal hemodynamic condition and maintain glomerular perfusion. Increased renal perfusion can also prevent tubular ischemia and ATN.[9,12]

Administration of dopamine during NTA is advantageous since it stimulates natriuresis and diuresis, and cleanses the tubulus from tubular sediments that can obstruct fluid movement in the lumen. This is very important, since it facilitates the process of repair of renal function and facilitates fluid administration.[9,12,14]

The Effect of Dopamine Administration on Acute Renal Failure

The effect of dopamine administration in the development of renal failure has been studied in many laboratory animals. The largest study is the creation of an ischemic renal model by tying the renal artery. Iania et al administered 6 mg/kg Bodyweight/minute of dopamine infusion for 15 to 30 minutes after tying the renal artery of rats for 70 minutes after nephrectomy of the contralateral kidney. The rat had low serum creatinine and urea levels and an increase in inulin clearance after 24 hours. From this study, it was concluded that the benefits of dopamine use is observable within the first 24 hours due to the immediate effect of the blockage of the renal artery. Pollock and Obgernorth studied the influence of dopamine in rats whose renal artery was tied for 30 minutes. Dopamine was administered at a dose of 10 mg/kg Bodyweight/minute for 1 hour after the tie was undone. There was no difference in serum creatinine level in the group who received the dopamine compared to control up to 4 days. The histological findings in both groups of animals were also identical.[3]

A similar study was conducted on dogs that received 3 mg/kg Bodyweight/minute of dopamine for 60 minutes after removal of the renal artery block. There was no GFR improvement.

Laboratory animals who suffered from man-made acute renal failure using gliceral solution causing rhabdomyolysis and nephrotoxic drugs were not reported to demonstrate a significant difference after administration of 1.6 to 5 mg/kg Bodyweight/minute of dopamine.

Dopamine has also been tried on various species models with various doses and time spans. No positive or negative effects were reported, making it difficult to conclude that there is a beneficial effect in the administration of dopamine in man.[3]

Use of Dopamine as a Preventive Measure

Dopamine may be used to prevent the development of acute renal failure in high risk patients. Nevertheless, studies that have been conducted had many shortcomings in the sample and control size as well as the use of different doses.[3,6]

In a prospective controlled randomized study on 37 patients who underwent surgery for abdominal aorta aneurism, Baldwin et al demonstrated no benefits in post-surgical dopamine administration. The same findings were reported from patients undergoing elective coronary heart surgery.

In patients who underwent liver transplantation, Polson et al reported a retrospective study on 36 patients, where 21 of them received preventive dopamine infusion (2 mg/kg Bodyweight/minute). There was an increase in the number of patients with olyguria in the group that did not receive dopamine, but the difference was not significant to the point needing dialysis. Swigerth conducted a prospective randomized study on 48 transplant patients who received 3 mg/kg Bodyweight/minute of dopamine. There was no difference in the serum creatinine level between the trial and control groups after 3 days, or in GFR value after 1 month.[3,11]

The Use of Dopamine In Acute Renal Failure

In 1970, Talley et al reported a serial study on 5 patients with acute renal failure olyguria who received a

combination of dopamine (4 mg/kg Bodyweight/ minute) and a diuretic agent, demonstrating improved renal function. In the same year, Barnardo et al demonstrated that dopamine increased the inulin clearance in 10 patients with liver cirrhosis and renal dysfunction. The best effect in dopamine administration was found in kidneys that were well functioning.[3,11,15,16]

Even though dopamine has been widely used for 3 decades as a treatment for acute renal failure, data that supports the benefit of the use of this drug is still unclear.[3,11]

Complications of Dopamine Administration

When administered in low doses, dopamine has several side effects, including tacchyarrythmia, increased left and right ventricular after load, respiratory depression, and increased intrapulmonary shunting. If dopamine is administered through the peripheral vein, extravasation may occur, causing local ischemia, or even necrosis. There are also risks of diuresis due to administration of dopamine in dehydrated patients. Dopamine also has an endocrinal effect, even though its significance is still unclear, and can also change the immune response by influencing T-cell proliferation.[13,14]

Bowel ischemia should also be considered in patients with multi system/organ failure. As a mesenteric vasodilator, dopamine is expected to reduce bowel ischemia. In 25 critical patients treated with dopamine, Maynard et al did not found the expected improvement in sphlancnic perfusion (red- this is the opposite of what is found in the abstract and conclusion).[3,13]

The influence of dopamine varies according to the dose. Based on normal human physiology, it is used to treat acute renal failure.

CONCLUSION

Administration of a certain drug should be considered based on the risks and benefits of the drug use.

Up to now, there is still no study on dopamine that produced a significant protective effect on the kidneys.[3]

Use of dopamine for preventive measures towards renal malfunction is not beneficial, but may be considered in patients with acute renal failure and early ATN (with a relatively good renal function) due to its diuretic effect.[3,11,15,16]

The side effects of dopamine administration, be it not fatal, should receive attention, since the complication occur at low doses. The side effect that may occur include tachycardia, arrhythmia, miocardiac ischemia, as well as bowel ischemia due to precapilary vasoconstriction causing bacterial translocation from the intestinal lumen to the systemic bloodflow.[3,13]

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