Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial

*Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group**

Summary

Background Low-dose dopamine is commonly administered to critically ill patients in the belief that it reduces the risk of renal failure by increasing renal blood flow. However, these effects have not been established in a large randomised controlled trial, and use of dopamine remains controversial. We have done a multicentre, randomised, double-blind, placebo-controlled study of low-dose dopamine in patients with at least two criteria for the systemic inflammatory response syndrome and clinical evidence of early renal dysfunction (oliguria or increase in serum creatinine concentration).

Methods 328 patients admitted to 23 participating intensive-care units (ICUs) were randomly assigned a continuous intravenous infusion of low-dose dopamine (2 μg kg^{-1} min^{-1}) or placebo administered through a central venous catheter while in the ICU. The primary endpoint was the peak serum creatinine concentration during the infusion. Analyses excluded four patients with major protocol violations.

Findings The groups assigned dopamine (n=161) and placebo (n=163) were similar in terms of baseline characteristics, renal function, and duration of trial infusion. There was no difference between the dopamine and placebo groups in peak serum creatinine concentration during treatment (245 [SD 144] *vs* 249 [147] μmol/L; p=0·93), in the increase from baseline to highest value during treatment (62 [107] *vs* 66 [108] μmol/L; p=0·82), or in the numbers of patients whose serum creatinine concentration exceeded 300 μmol/L (56 *vs* 56; p=0·92) or who required renal replacement therapy (35 *vs* 40; p=0·55). Durations of ICU stay (13 [14] *vs* 14 [15] days; p=0·67) and of hospital stay (29 [27] *vs* 33 [39] days; p=0·29) were also similar. There were 69 deaths in the dopamine group and 66 in the placebo group.

Interpretation Administration of low-dose dopamine by continuous intravenous infusion to critically ill patients at risk of renal failure does not confer clinically significant protection from renal dysfunction.

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Introduction

Physicians and surgeons in many countries commonly use low-dose dopamine in critically ill patients because, in healthy volunteers, it increases renal blood flow and induces natriuresis and diuresis.[1,2] Although these haemodynamic and diuretic effects are expected to afford a clinically significant degree of renal protection in patients at risk of acute renal failure,[3] no large controlled trials have been done to test whether administration of dopamine attenuates renal injury.[4] Furthermore, there is concern about the potential adverse effects of low-dose dopamine on pituitary function, T-cell responsiveness, and gastrointestinal oxygenation.[5–7] We undertook a multicentre, randomised, double-blind, placebo-controlled trial of low-dose dopamine infusion in intensive-care-unit (ICU) patients at risk of acute renal failure to assess whether dopamine attenuated the rise in serum creatinine.

Methods

Patients

Between March, 1996, and April, 1999, we screened patients admitted to 23 participating ICUs to identify adult patients who met our inclusion criteria. These criteria were: presence of a central venous catheter; two or more of the pathophysiological changes of the systemic inflammatory syndrome (SIRS)[8] over a 24 h period; and at least one indicator of early renal dysfunction (urine output averaging <0·5 mL/kg hourly over 4 h or longer; serum creatinine concentration >150 μmol/L in the absence of premorbid renal dysfunction; a rise in serum creatinine concentration of >80 μmol/L in less than 24 h in the absence of creatine kinase >5000 IU/L or myoglobin in the urine).

Exclusion criteria were: age under 18 years; an episode of acute renal failure within the previous 3 months; previous renal transplantation; use of dopamine at any dose during the current hospital stay; baseline serum creatinine concentration above 300 μmol/L; enrolling physician's belief that the drug could not be administered for 8 h or longer; and unsuitability for use of renal replacement therapy.

Permission to proceed with the trial was obtained from the institutional ethics committee of each participating unit. Patients or their next of kin gave informed consent to participate in the trial. In two institutions, the need for informed consent was waived by the ethics committee, which simply requested that the patient or family be informed of inclusion in the trial.

Design and procedures

Patients were randomly assigned to study groups in blocks of ten with stratification according to centre by a centralised masked-draw system that combined coded numbers with drug allocation. Each block of ten numbers was transmitted from the central office to a person who acted as the randomisation authority in each centre. This

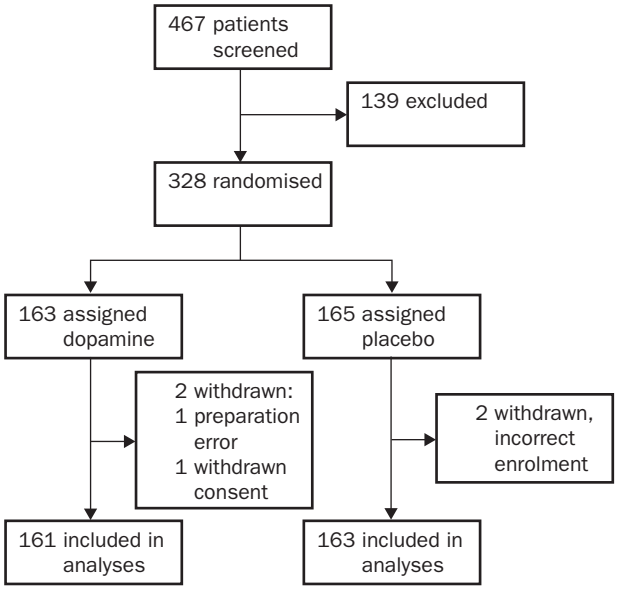


Figure 1: **Trial profile**

Characteristic	Dopamine (n=161)	Placebo (n=163)
Demography		
Age (years)*	63 (15)	61 (17)
Male/female†	94/67	102/61
Condition		
Admission APACHE II score*	21 (6)	21 (8)
Admission SAPS II score*	43 (14)	45 (16)
APACHE II score at start of infusion*	18 (7)	18 (7)
SAPS II score at start of infusion*	40 (15)	41 (15)
Shock‡ at start of infusion†	93	102
On ventilator at start of infusion†	138	141
Type of admission†		
Respiratory, medical	32	25
General, surgical	30	35
Vascular, surgical	19	16
Cardiac, surgical	12	12
Multiple trauma	8	14
Cardiac, medical	4	12
General, medical	13	6
Haematology/oncology	8	7
Gastrointestinal, medical	7	6
Thoracic, surgical	5	6
Other, medical	8	9
Other, surgical	15	15
Renal characteristics		
Pre-renal renal dysfunction†	152	154
Nephrotoxic component†	9	9
Baseline creatinine (μmol/L)*	183 (85)	182 (81)
Baseline urea (mmol/L)*	14·3 (7·5)	14·4 (7·1)
Oliguria†	109	113
Haemodynamics		
Mean arterial pressure (mm Hg)*	80 (15)	80 (16)
Central venous pressure (mm Hg)	14 (8)	13 (7)

*Mean (SD). †Number of patients. ‡Need for continuous intravenous infusion of catecholamines or phosphodiesterase inhibitors to support the circulation.

Table 1: **Baseline characteristics of study participants**

individual (a pharmacist or a nurse not involved in care of the trial patients and independent of the site investigator) was responsible for allocation, preparation, and accounting of trial infusion. The trial infusion was prepared at a separate site, then taken to the bedside nurse every 24 h. The nurse infused it into the patient at the appropriate rate. The randomisation schedule was thus concealed from all care providers, ward physicians, and other research personnel.

No patient, research nurse, investigator, or any other medical or nursing staff in the ICU was aware of the treatment assignments for the duration of the study. All statistical analysis was also done with masking maintained. Randomisation authorities were instructed to report any suspected breach of the masking procedures. No report was filed.

The drug or placebo (vehicle without active drug) was prepared for syringe pump infusion or for volumetric pump infusion in indistinguishable syringes or bags. The study protocol required that the trial preparation be infused continuously at 2 $\mu g\ kg^{-1}\ min^{-1}$ (or the equivalent volume for placebo) until one of the following events occurred: the patient was given renal replacement therapy; the patient died; a serious adverse event developed that was judged to be related to the trial infusion; the patient's SIRS and renal dysfunction had resolved for at least 24 h; and the patient was discharged from ICU. At that point the trial infusion was stopped.

We documented each patient's age, sex, institution, diagnostic category, major trigger for the development of acute renal dysfunction, SIRS criteria, renal dysfunction criteria, baseline urine output, mean arterial pressure, and central venous pressure at the time of enrolment; mean arterial and central venous pressure when the trial infusion was started; use and dose of vasoactive drugs; use of loop diuretics; and APACHE II (acute physiology and chronic health evaluation)[9] and SAPS II (simplified acute physiology score)[10] at admission and at enrolment.

The primary outcome measure for the study was the peak serum creatinine concentration reached during trial infusion. Secondary outcome measures included reason for cessation of trial infusion, the development of cardiac arrhythmias, the durations of mechanical ventilation, ICU stay, and hospital stay, peak plasma urea concentration reached during the trial infusion, the change in serum creatinine and urea concentrations from baseline to peak value, the hourly urine output at predefined times, the number of patients who needed renal replacement therapy, the number of patients whose serum creatinine concentration exceeded 300 μmol/L, survival to ICU discharge, and survival to hospital discharge.

Statistical analysis

The peak serum creatinine concentration during trial infusion was chosen as the primary outcome measure because we judged it a clinically appropriate measure of glomerular filtration rate. We assumed that this primary outcome variable would have a normal distribution and an SD equal to 60% of its mean. The mean value estimated for the control group was 250 μmol/L. These estimates were based on information obtained from a pretrial observational study in six participating units of the natural course of early renal dysfunction as defined in this study. For the trial to have 80% power of detecting a 20% decrease in peak serum creatinine with low-dose dopamine, at α=0·05, we calculated that 115 patients in each group would be needed. After two planned interim analyses, with masking maintained, at 100 and then 200 patients, the size of the trial was increased to more than 300 patients to increase its statistical power. From the final SD for the control and intervention groups, this study had 90% power to detect a difference of more than 25% in peak serum creatinine between the groups at an α of 0·05.

We used a statistical software package (Statview, version 4.5) for analyses. The distribution of data was tested for normality before analysis. When the criteria for normal distribution were not met, non-parametric methods were used for comparisons. Between-group comparisons for numerical values were therefore done by either Student's

	Dopamine (n=161)	Placebo (n=163)	Difference (95% CI)
Serum concentrations*			
Peak creatinine (μmol/L)	245 (144)	249 (147)	4 (−28 to 36)
Peak urea (mmol/L)	20 (10)	23 (12)	3 (−0·8 to 6·8)
Increase in creatinine (μmol/L)	62 (107)	66 (108)	4 (−21 to 29)
Increase in urea (mmol/L)	6 (8)	7 (9)	1 ((−1 to 3)
Number of patients with event			
Creatinine concentration >300 μmol/L	56	56	0 (−16 to 16)
Renal replacement therapy	35	40	5 (−10 to 20)
Urine output (mL/h)*			
Baseline	37 (40)	50 (59)	13 (−1 to 27)
After 1 h	71 (81)	72 (77)	1 (−20 to 22)
After 24 h	96 (101)†	92 (72)†	4 (−19 to 27)
After 48 h	99 (83)†	109 (95)†	10 (−11 to 31)

*Mean (SD). †Significantly greater than baseline value (p=0·006).

Table 2: **Effect of trial infusion on markers of renal function**

t test or the Mann-Whitney *U* test. Changes in urine output over time were not normally distributed and were compared by ANOVA (Friedman's test) followed by post-hoc pairwise comparison with Wilcoxon's signed-rank test adjusted for multiple comparisons. Comparison of nominal measures was by Fisher's exact test. Comparison of time from initiation of treatment to event (survival analysis) was by the Mantel-Cox test.

Results

The trial enrolled 328 patients (figure 1). Four patients were excluded from analysis (one withdrew consent, one received infusion of both placebo and dopamine owing to a preparation mistake, and two were enrolled on the basis of an incorrect serum creatinine and had not met entry criteria). There were five minor protocol violations, which involved slight pauses in the infusion of the trial drug. These patients were included in data analysis. Their inclusion in or exclusion from data analysis did not affect the findings.

The baseline characteristics of the 324 patients included in the analyses are given in table 1. The two groups were well matched for illness severity and other clinical characteristics. No patient had parenchymal disease or obstruction. After randomisation, low-dose dopamine was infused for a mean of 113 h (SD 157) and placebo was infused for a mean of 125 h (166; p=0·45).

During trial infusion, serum creatinine and urea concentrations and urine output increased similarly in both groups (table 2). The increase in urine output may have been related partly to the simultaneous administration of loop diuretics to 90 patients in each group. The mean dose of furosemide per patient was 192 mg (256) in the dopamine group and 268 mg (314) in the placebo group (p=0·39).

There were no differences in secondary outcome measures. The duration of mechanical ventilation was similar for both groups (10 [13] *vs* 11[14] days; p=0·63). There was no difference in the duration of ICU stay (13 [14] *vs* 14 [15] days; p=0·67) or hospital stay (29 [27] *vs* 33 [39] days; p=0·29). Cardiac arrhythmias were common in both groups; most were supraventricular, and atrial fibrillation was the most common. 53 patients in the dopamine group and 54 in the placebo group experienced arrhythmias.

Survival to ICU discharge (108 *vs* 105 patients; p=0·61) and survival to hospital discharge (92 *vs* 97 patients; p=0·66) were similar in the randomised groups. When patients who stopped dopamine or placebo because of resolution of renal dysfunction were separately analysed, no difference in time to renal recovery was found (figure 2).

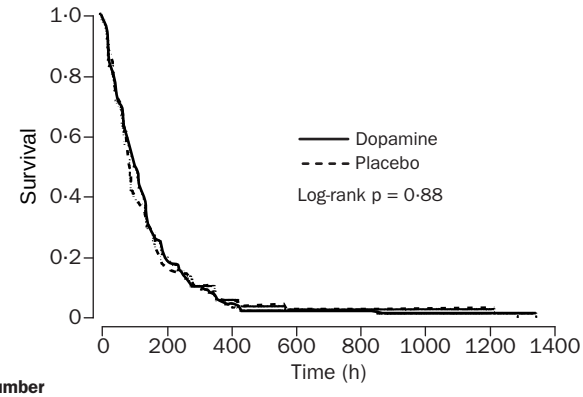
Low-dose dopamine was stopped in seven patients because the trial drug was thought to have precipitated the sudden onset of arrhythmia. Placebo was stopped in seven patients for the same reason. There were no significant differences in the number of patients who received nephrotoxic drugs during dopamine or placebo infusion. Vancomycin was given to 24 patients in the dopamine group and 21 in the placebo group, aminoglycosides to 31 and 36, radiocontrast agents to three patients in each group, and amphotericin B to one patient in the dopamine group and three in the placebo group.

Discussion

Low-dose dopamine is commonly given to patients judged to be at risk of renal failure, to increase renal blood flow and preserve glomerular filtration rate,[11] because it has these effects when infused intravenously in healthy volunteers.[12] Renal ischaemia may be the commonest cause of acute renal failure.[13] Low-dose dopamine would therefore be expected to increase renal blood flow and help preserve renal cellular oxygenation, glomerular filtration rate, and urine output. These beneficial effects would then prevent acute renal failure. However, dopamine is also a proximal-tubular diuretic, so it increases the presentation and reabsorption of chloride by the ascending limb of the loop of Henle. This effect may inadvertently increase medullary oxygen consumption and exacerbate medullary ischaemia.

Several studies in animals have investigated the effect of dopamine as a renal protective drug.[11] However, in none was dopamine (<3 μg kg^{-1} min^{-1}) the sole nephro-protective agent. Thus, no conclusions can be drawn about the effectiveness of this drug. Furthermore, any beneficial effects reported were associated with doses higher than 3 μg kg^{-1} min^{-1}. At such doses, dopamine has a systemic β-adrenergic effect with increases in cardiac output, heart rate, and blood pressure.[11] Such changes in systemic haemodynamics can be achieved with other β-adrenergic agents (dobutamine or dopexamine), are not unique to dopamine, and are likely to affect renal blood flow indirectly. Indeed, even at infusion rates of less than 3 μg kg^{-1} min^{-1}, dopamine may have substantial systemic haemodynamic effects.

Low-dose dopamine has also been investigated in the prevention of renal failure in high-risk clinical settings.[14–23] However, none of these clinical studies had sufficient



Number at risk

Dopamine	97	16	4	2	2	1	1	0
Placebo	87	16	5	2	2	2	2	0

Figure 2: **Kaplan-Meier curve of time to recovery of normal renal function for patients in whom the trial drug was stopped for that reason**

statistical power to detect any beneficial effect of low-dose dopamine. Furthermore, only a few were randomised, double-blind, and placebo-controlled, and 'low-dose' dopamine was given at 3 μg kg^{-1} min^{-1} in most. At such infusion rates, measurements of central haemodynamics clearly show systemic β-adrenergic effects on heart rate and cardiac output.[15] Any beneficial effect that may occur under such circumstances would then not be unique to dopamine but would most likely reflect the impact of increased cardiac output on renal blood flow. Indeed, in a randomised, controlled, double-blind crossover comparison, low-dose dobutamine (200 μg/min) improved glomerular filtration rate but dopamine did not.[24]

Doubts about the efficacy of low-dose dopamine as a renal protective agent have been counterbalanced by the perception that it is extremely safe. Lately, however, doubts about safety have also been raised. Dopamine decreases serum prolactin concentrations and, thereby, induces a transient decrease in T-cell function,[6] which may impair resistance to infection. Dopamine also decreases growth-hormone secretion and thyrotropin release.[5] Growth-hormone deficiency can contribute to a negative nitrogen balance in critical illness. Low-dose dopamine contributed to mucosal hypoxia in an experimental model of haemorrhagic shock.[7] Other adverse effects include depression of respiratory drive and a proarrhythmic effect.[11] These effects are unpredictable because dopamine clearance and metabolism are altered in acutely ill patients, leading to extreme variability in plasma dopamine concentrations even at steady-state infusion rates.[25,26] Controversy about the administration of low-dose dopamine is therefore not surprising.[3,4,27–29]

Our study, which had sufficient statistical power to detect a small change in glomerular filtration rate, found that the peak serum creatinine concentration was similar in the dopamine and placebo groups. No differences were found in other clinical markers of renal function. These findings support the view that low-dose dopamine dos not confer a clinically significant degree of renal protection in critically ill patients, with SIRS, at risk of renal failure.

Our investigation did not address the issue of the efficacy of low-dose dopamine as a prophylactic agent. Low-dose dopamine may be more effective when prescribed before any potential renal stress than when used for rescue during early renal dysfunction. However, none of the four small randomised trials that have used dopamine prophylactically showed any benefit. A benefit might have been apparent if dopamine had been given at higher doses, but at these doses the drug has predictable systemic β-adrenergic effects (as discussed above).[15] Our aim was not to study the effects of increasing cardiac output on renal function.

The average duration of infusion in our patients was longer than 4 days. This duration seems sufficient to give low-dose dopamine a chance to produce beneficial effects. The measurement of renal function in ICU patients is difficult. Dopamine may confer physiological benefits to the kidneys that are not clinically apparent or measurable with routine tests of renal function. However, maintenance of glomerular filtration rate and urine output are the typical primary goals of clinical intervention, so a drug that does not include beneficial changes in these variables is unlikely to provide appreciable benefit to the patient.

If low-dose dopamine were given to patients with a low background frequency of renal dysfunction, its benefits might not become apparent. However, about 25% of our patients eventually required renal replacement therapy. Thus, the study population was appropriate for the investigation of a nephroprotective agent. The need for renal replacement therapy may be a more desirable primary outcome measure for a trial such as this. However, renal replacement therapy is typically initiated in ICU because of insufficient urine output, causing volume overload, or because of large falls in glomerular filtration rate causing uraemia, hyperkalaemia, and acidaemia. An agent that did not affect urine output or serum creatinine concentrations seems unlikely to decrease the use of renal replacement therapy. Furthermore, if the absolute difference seen in this study (3%) was not a chance finding but a true difference in favour of dopamine, a study would have to enrol 9000 patients to have 90% power to detect such a difference at $\alpha=0{\cdot}05$.

The population studied is only representative of ICU patients. In less ill patients who are at risk of renal dysfunction or who show early signs of renal injury in the general wards, low-dose dopamine may prove beneficial. However, in that population, which is likely to experience more subtle changes in glomerular filtration rate or urine output, a much larger group of patients would have to be studied. The mortality rate among our patients was high. The lack of effect of low-dose dopamine may have been due to less than optimum resuscitation or general care. This explanation seems unlikely. The mean arterial pressure and central venous pressure at enrolment and infusion of the study preparation seemed to reflect optimum intravascular filling and maintenance of perfusion pressure. Furthermore, mortality was below that predicted by the illness severity scores calculated on admission. Finally, we did not attempt to control the prescription of other drugs that may affect urine output or glomerular filtration rate, such as loop diuretics or vasoactive drugs, because we wished to test the effect of low-dose dopamine in a clinical environment that was representative of current practice. However, these agents were administered with almost identical frequency in the two groups and are unlikely to have affected our findings.

Almost 25% of these critically ill patients with SIRS and oliguria or a rising serum creatinine concentration needed renal replacement therapy and more than 40% died. The need for effective nephroprotective agents remains.

ANZICS Clinical Trials Group

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