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## Comparative Study of Dopamine and Mannitol Effects on Renal Function During Cardiopulmonary Bypass by Using N-acetyl- $\beta$ -D-glucosaminidase Assay\*

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**Abstract:** The protective roles of low-dose dopamine and mannitol infusion in the renal function of patients undergoing cardiovascular surgery were compared in 36 patients by measuring urine N-acetyl- $\beta$ -D-glucosaminidase activity, serum and urinary creatinine, blood urea nitrogen (BUN) levels and urine output. The patients were randomly selected and received a continuous infusion of dopamine, 3  $\mu$ g/kg/min (Group I), mannitol, 1 mg/kg/h (Group II), no medication (Group III) before the induction of anaesthesia. Urine N-acetyl- $\beta$ -D-glucosaminidase activities, serum and urinary creatinine and BUN were determined preoperatively after aortic cross-clamping, and on the first and second

postoperative days. Changes in urine N-acetyl- $\beta$ -D-glucosaminidase activity or serum and urinary creatinine, and BUN levels were not statistically significant ( $p>0.05$ ) between different groups. Our results revealed that, for the protection of renal function during cardiopulmonary bypass, on comparison, the prophylactic use of "low-dose" dopamine or mannitol did not display any marked superiority.

**Key Words:** Kidney: function. Enzyme: N-acetyl- $\beta$ -D-glucosaminidase. Pharmacology: dopamine, mannitol. Surgery: cardiopulmonary bypass

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### Introduction

Renal hypoperfusion affects the kidney during cardiopulmonary bypass (CPB) surgery and may result in acute renal failure (1-3). The incidence of renal failure in cardiovascular surgery varies in the range 2.5-31%. Oliguric renal failure increases postoperative mortality to 67% in patients undergoing cardiac surgery (4, 5). In order to prevent acute renal failure, several diuretics (such as mannitol and frusemide) and inotropic agents (such as dopamine and dobutamine) have been used prophylactically (6). These agents have been shown to protect the kidney from ischemic damage by different mechanisms. It is thought that mannitol improves renal plasma flow, increases urine output and possibly acts as a free radical scavenger (7, 8). The protective effect of dopamine is thought to be a result of its selective action on renal DA1 receptors that increase renal blood flow, glomerular filtration rate, sodium excretion and urine output (9, 10). However, which one of them offers better protection for the kidney is not clear.

In recent years, a lysosomal enzyme, N-acetyl- $\beta$ -D-glucosaminidase (NAG), which is located predominantly in the proximal renal tubules, has been indicated as a marker for the diagnosis and follow-up of the clinical course of various renal diseases and renal lesions (11). Functional alterations of tubular origin can be evaluated by measuring NAG activity (12). NAG activity increases with kidney damage, and it is considered to be a sensitive index of renal disease. It has been used for early diagnosis of kidney and urinary tract pathologies such as drug nephrotoxicity, rejection in renal transplantation, acute tubular necrosis, glomerulonephritis and obstructive uropathy (13, 14).

We investigated the protective effects of prophylactic "low-dose" dopamine and mannitol administration on renal function in patients subjected to CPB by measuring urine NAG activity, serum and urinary creatinine, and BUN.

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## Materials and Methods

Thirty-six hospitalized patients with an average age of 53.7 years (range 35-70 y), who underwent elective coronary artery surgery were included in the study. This study was approved by the ethics review board of the hospital. None of the patients were diabetic and all had normal renal function. The exclusion criteria for this study were the following: (i) serum creatinine levels greater than 1.3 mg/dl, (ii) BUN greater than 60 mg/dl, (iii) severe hypertension, (iv) presence of any carotid or peripheral artery disease, (v) left ventricular ejection fraction lower than 50%, and (vi) contact with any radiocontrast agent (as in a diagnostic procedure) within 72 hours of surgical procedure. None of the patients reported any history of clinical renal dysfunction or failure.

The patients were randomly allocated into 1 of 3 groups using opaque sealed envelopes. Each group contained 12 patients, with Group I being given "low-dose" dopamine, Group II being given mannitol, and Group III receiving no treatment during the surgical procedure. Premedication consisted of oral diazepam (10 mg), 1 hour before the operation. Anaesthesia was induced with fentanyl (10  $\mu$ g/kg iv), propofol (2 mg/kg iv) and vecuronium (0.06 mg/kg iv) in each group and maintained with O<sub>2</sub> and N<sub>2</sub>O (50%-50%) and isoflurane (0.8%-1%). Cefazolin sodium and gentamicin prophylaxis were used during the induction of anaesthesia. Dopamine infusion (3  $\mu$ g/kg/min) was started in Group I, while 20% mannitol infusion (1 mg/kg/h) was started in Group II immediately after the induction of anaesthesia and the insertion of a central venous catheter, and given continuously throughout the CPB. Drug infusion was discontinued at the end of skin closure.

Normal saline (0.9%) was used intraoperatively (4-5 ml/kg/h) and postoperatively (2 ml/kg/h). No other drugs were used for inotropic support or diuresis during the operation. The CPB circuit incorporated a disposable membrane oxygenator with nonpulsatile flow, and the priming solution was prepared with 2 L Ringer's lactate solution without mannitol. Moderate hypothermia was applied at 26°C. The mean arterial pressure was maintained at 50-70 mmHg throughout the CPB.

Blood and urine samples were obtained at four different times: before the induction of anaesthesia, after the application of a cross-clamp to the aorta, and on the first and second postoperative days. These samples were used for the determination of NAG activity, levels of serum and urinary creatinine, and BUN. The CPB and aorta cross-

clamp times were determined. Urine volume was measured during the operation and on the first postoperative day.

### Enzyme assay

The urine samples were stored at -20°C and assayed within at least 20 days. NAG activity was determined by measuring the ability of a urine sample to hydrolyze p-nitrophenyl-N-acetyl- $\beta$ -D-glucosaminide to p-nitrophenol for 15 minutes at 37°C and monitoring the formation of p-nitrophenol product at 405 nm. A unit of activity was defined as  $\mu$ mol p-nitrophenol per minute under the assay conditions. The specific activity of the enzyme was calculated according to the urine creatinine level and expressed as U/gr creatinine (14). All the samples were examined by the same biochemistry specialist, blind as to the identity and purpose of the analyzed samples.

Serum and urinary creatinine, and BUN were measured on an ASTRA-8 autoanalyzer (Beckman Instruments) by the standard automatic assay methods.

### Statistics

Since the NAG values were distributed non-normally, logarithmic transformation was performed and log(NAG) values were used for all further calculations. Age, body weight, pump duration, clamp time, urinary output and baseline log(NAG), serum and urinary creatinine, and BUN were compared by one-way analysis of variance (ANOVA) with Tukey's HSD test for pairwise group comparisons.

Repeated-measures ANOVA with one within-subject effect (group effect) and one dependent variable was performed in order to evaluate the changes with time and the parallelism of curves against time of the log (NAG), serum and urinary creatinine, and BUN values. The p values for time effect and group effect were calculated by the Hotellings test. Statistical significance was assigned to p values less than 0.05. The statistical Package for Social Sciences (SPSS) for Windows, version 5.01, was used for all calculations.

## Results

The characteristics of the patient group, and the time periods of the CPB procedure and aortic cross-clamping are given in Table I. There were no significant differences among the groups for any parameter given in the table.

There were no statistically significant differences in the concentrations of serum BUN, creatinine, and urinary creatinine levels and urine outputs in the three groups

(Table 2 and Table 3). Urine outputs could be measured only perioperatively and on the first postoperative day, because the urinary catheter was removed on the second postoperative day.

The figure shows the activity of NAG in urine sample before and during the operation, and on the first and second postoperative days. A comparison of the urinary NAG activities did not show any significant differences in the 3 groups ( $p>0.05$ ) (Figure).

Table 1. The distribution of the patients with regard to age, sex and body weight with periods of CPB and aortic cross-clamping (mean  $\pm$ SD).

	Dopamine (Group I)	Mannitol (Group II)	Control (Group III)
Age (year)	53.2 $\pm$ 10.9	55.4 $\pm$ 8.4	53.7 $\pm$ 8.3
Sex (F/M)	4/8	3/9	6/6
Body weight (kg)	72.8 $\pm$ 10.3	77.4 $\pm$ 8.4	71.6 $\pm$ 8.1
CPB (min)	48.4 $\pm$ 4.9	45.1 $\pm$ 3.6	59.5 $\pm$ 5.4
Cross-clamp (min)	28.9 $\pm$ 2.4	26.4 $\pm$ 2.4	31.9 $\pm$ 3.6

( $p>0.05$ )

Table 3. Urine out put (mg/kg/h) (mean $\pm$ SD).

	perioperative	1 <sup>st</sup> postoperative day
Dopamine (Group I)	1.9 $\pm$ 0.8	1.8 $\pm$ 0.2
Mannitol (Group II)	1.6 $\pm$ 0.4	1.7 $\pm$ 0.4
Control (Group III)	1.3 $\pm$ 0.1	1.7 $\pm$ 0.2

( $p>0.05$ )

Table 2. Serum BUN (mg/dl) and creatinine (CRE) (mg/dl) levels in the three groups (mean $\pm$ SD).

	Dopamine (Group I)		Mannitol (Group II)		Control (Group III)	
	BUN	CRE	BUN	CRE	BUN	CRE
preinduction	16.5 $\pm$ 4.7	1.3 $\pm$ 0.9	17.1 $\pm$ 5.1	1.0 $\pm$ 0.2	12.5 $\pm$ 4.5	0.9 $\pm$ 0.2
CPB	15.7 $\pm$ 4.3	1.1 $\pm$ 0.3	16.5 $\pm$ 6.0	1.0 $\pm$ 0.2	13.2 $\pm$ 5.6	0.9 $\pm$ 0.2
1 <sup>st</sup> postop day	15.4 $\pm$ 6.1	1.1 $\pm$ 0.4	15.3 $\pm$ 9.3	1.2 $\pm$ 0.6	14.3 $\pm$ 5.7	1.1 $\pm$ 0.3
2 <sup>nd</sup> postop day	13.7 $\pm$ 3.9	1.1 $\pm$ 0.2	14.2 $\pm$ 11.4	1.2 $\pm$ 0.5	18.2 $\pm$ 7.5	1.1 $\pm$ 0.2

( $p>0.05$ )

### Discussion

We compared an inotropic agent (dopamine) with a diuretic (mannitol) in a controlled and blind study, with respect to their renal protective effects during CPB. Our results showed no advantage in the use of either "low-dose" dopamine (3  $\mu$ g/kg/min) or mannitol (20%) compared to a no-treatment control in the absence of therapy with other inotropic or diuretic agents. One of the reasons why we were unable to identify any difference (if, in fact, a difference exists) might be the number of patients. One possible cause of the failure to observe differences among the groups may be the limitations presented by a small group size, a constraint imposed by ethical considerations, as well as by a choice limited to patients at low risk for adverse renal outcomes subsequent to CPB.

In recent years, mannitol has been used prophylactically to prevent postischemic renal injury (7,15,16). However, mannitol administration for protecting the kid-

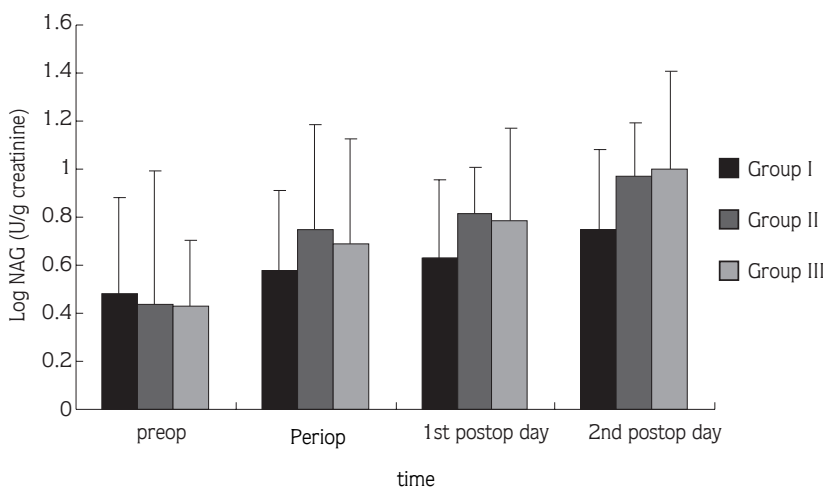


Figure: Comparison of the mean urine log (NAG) activity (mean $\pm$  SD). Group I= Dopamine, Group II=Mannitol; Group III= Control.

ney from ischemic damage in cardiac surgery is still a controversial area. It has the disadvantage of undesirable volume loading (6). Recently, Ip-Yam et al. (7) found that mannitol had no significant effects in patients without previous renal impairment who underwent CPB surgery. Our results showed that the mannitol group was no different from the dopamine and control groups during CPB surgery. Nevertheless, dopamine is commonly used to prevent acute tubular necrosis. There is only one study in the literature in which dopamine was found to protect against radiocontrast-induced renal failure in patients with pre-existing renal impairment (17).

The serum BUN, creatinine and urinary creatinine levels did not change in any of the 3 groups. Although the most frequently used indicators of renal function after surgery are urine output and serum creatinine, urinary NAG is a more sensitive test in monitoring renal function (18). Increased levels of urinary NAG activity indicate early changes in renal tubules. In our study, urinary NAG activity did not change during or after operation with "low-dose" dopamine or mannitol, and no side effects were observed in our patients. Neither urine output nor creatinine increased in any of the 3 groups. To this end, it must be pointed out that one of the characteristics of

the kidney is its ability to compensate for damage, and, therefore, classical renal function tests are insensitive, since their levels change only when there is a large reduction in effective nephron mass (18).

While some previous studies (17, 19) showed that infusion of "low-dose" dopamine or mannitol maintained renal function or minimized the ill effects of trauma presented by CPB, the findings in our study support the conclusions of other work (7, 20-22) in which dopamine or mannitol treatment provided no aid whatsoever in compensating for damage caused by the procedure.

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