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Perioperative fenoldopam for the prevention of acute renal failure in non-cardiac surgery, randomized clinical trial

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ABSTRACT

Purpose. Acute renal failure is a serious complication of surgery causing morbidity and mortality. The aim of this study was to evaluate the efficacy of fenoldopam, a selective dopamine-1 receptor agonist, in patients at high risk of perioperative renal dysfunction.

Methods. In this prospective single-center randomized double-blind trial we enrolled 64 patients undergoing major surgery. Patients received either fenoldopam at a dosage of 0.05 mcg/kg/min or dopamine at a dosage of 2.5 mcg/kg/min after anesthesia induction for a 12-hour period. The primary endpoint was defined as 25% serum creatinine increase from baseline after surgery.

Results. All the patients included were at high risk of perioperative renal dysfunction and underwent major surgery. The two groups (fenoldopam versus dopamine) were homogenous cohorts and no difference in outcome was observed. The incidence of acute renal failure was similar: 11/32 (34%) in the fenoldopam group and 14/32 (44%) in the dopamine group (p=0.6). The postoperative serum creatinine peak was also similar in the two groups. No in-hospital death was observed.

Conclusion. Despite an increasing number of reports suggesting renal protective properties of fenoldopam, we observed no difference in clinical outcome compared to dopamine in a high-risk population undergoing major surgery.

Key words: fenoldopam, acute renal failure, major surgery, serum creatinine

Introduction

Acute renal failure (ARF) is a serious complication of surgery and is associated with significant in-hospital and long-term morbidity and mortality, as well as prolonged hospital stay.

Fenoldopam mesylate, a benzazepine derivative, is the first selective dopamine-1-receptor agonist approved for clinical use (in hypertensive urgencies and emergencies). The selective dopaminergic action of fenoldopam appears to improve renal performance when renal blood flow is reduced such as in severe hypertension, (1,2) hypertensive patients with pre-existing impaired renal function (3) and ventilation with positive end-expiratory pressure. (4) These effects are mediated by an increased renal blood flow to both cortex and medullary regions.

Recent meta-analyses (5,6) and controlled studies (both case-matched (7) and randomized (8)) suggested that fenoldopam could be effective in the prevention and treatment of ARF. Other

Table 1. Clinical characteristics and preoperative data of 64 patients who received either fenoldopam (n=32) or dopamine (n=32) to prevent perioperative acute renal failure.

Variables	Fenoldopam	Dopamine
Weight, Kg	78±10.5	73±11.1
Age, yr median (range)	68 (30-79)	69 (29-80)
Creatinine, μmol/l	114±53	114±53
Heart Rate baseline, beats per minute	70±12.3	72±12.8
Systolic Pressure baseline, mmHg	132±23.0	119±19.2
Diastolic Pressure baseline, mmHg	71±19.8	63±11.7
Central Venous Pressure baseline, mmHg	9±3.8	8±3.3

Table 2. Intra-operative data of 64 patients who received either fenoldopam (n=32) or dopamine (n=32) to prevent perioperative acute renal failure.

Variables	Fenoldopam	Dopamine	p
Intraoperative Urinary Output, ml	1897±298	1731±235	0.2
Urinary Output (first 24 hours), ml	3205±1033	2827±1387	0.2
Need for intra-operative diuretics, n of patients (%)	9 (28%)	11 (34%)	0.8
Hearth Rate t=1, beats per minute	70±11.3	71±8.6	0.6
Hearth Rate t=2, beats per minute	70±11.8	70±10.4	0.9
Hearth Rate t=3, beats per minute	70±11.2	72±12.7	0.6
Hearth Rate t=4, beats per minute	73±9.4	71±8.5	0.6
Systolic Pressure t=1, mmHg	116±16.9	114±18.8	0.6
Systolic Pressure t=2, mmHg	113±13.4	118±17.8	0.3
Systolic Pressure t=3, mmHg	117±13.8	116±17.1	0.9
Systolic Pressure t=4, mmHg	118±17.4	118±16.2	0.9
Diastolic Pressure t=1, mmHg	66±11.2	63±8.4	0.2
Diastolic Pressure t=2, mmHg	63±10.1	65±9.5	0.5
Diastolic Pressure t=3, mmHg	63±8.9	64±7.6	0.6
Diastolic Pressure t=4, mmHg	63±9.4	64±11.4	0.8
Vasoconstrictors, n of patients (%)	6 (19%)	7 (22%)	0.9

t1- 5 minutes after induction of anesthesia, T2 - 30 minutes after starting the study drug,
t3 - at the end of surgery, T4 - before leaving the theatre

Table 3. Post-operative data of 64 patients who received either fenoldopam (n=32) or dopamine (n=32) to prevent perioperative acute renal failure.

Variables	Fenoldopam	Dopamine	p
Acute renal failure (25% creatinine increase), n (%)	11 (34%)	14 (44%)	0.6
Acute renal failure (50% creatinine increase), n (%)	4 (12%)	7 (22%)	0.5
Acute renal failure (100% creatinine increase), n (%)	1 (3%)	3 (9%)	0.3
Furosemide, n of patients (%)	9 (28%)	11 (34%)	0.8
Postoperative serum creatinine (end of surgery), μmol/l	123±53	114±53	0.7
Postoperative serum creatinine (day 1), μmol/l	158±167	141±70	0.6
Postoperative serum creatinine (day 2), μmol/l	132±62	158±97	0.2
Peak post-operative serum creatinine, μmol/l	158±167	150±88	0.7

studies showed, on the contrary, no beneficial effect of this drug, (9,10) so there is still virtually no definitive evidence of its efficacy, especially in non-cardiac surgery. We therefore performed a prospective, randomized, double-blinded clinical trial in order to evaluate the renoprotective action of fenoldopam in a selected group of patients undergoing major surgery.

Materials and methods

The study was carried out according to the principles of the Declaration of Helsinki. The ethical committee of San Raffaele Hospital (Milano, Italy) approved the study protocol. All patients were provided with written information and signed a written informed consent.

Sixty-four consecutive eligible patients, 18 years of age or older, scheduled for urologic or vascular surgery at a tertiary university hospital were randomly assigned to receive either fenoldopam or dopamine.

We included patients at high risk of perioperative renal dysfunction such as patients undergoing nephrectomy plus removal of a controlateral tumor (in an urologic setting) or patients undergoing vascular surgery with aortic cross-clamp who presented with a preoperative serum creatinine $> 123\ \mu$mol/l.

Conversely, exclusion criteria included an emergency procedure, preoperative dialysis, glaucoma (to avoid the risk of increasing intra-ocular pressure associated with fenoldopam administration) and a previous adverse reaction to fenoldopam or its infusion components (metabisulfite or sulfitesprevious).

Subjects were allocated according to randomization derived from a computer-generated list of random numbers, with no blocking, by an independent statistician. The details of the randomization were contained in a set of sealed opaque envelopes. These were available only shortly before anesthesia induction and were opened by independent research nurses that were not further involved in patients' management or follow up. Participants, care providers, and those assessing outcomes were all blinded to the assigned study drug.

Of the 85 eligible patients, 21 refused to sign the informed consent and did not take part in the study (figure 1). 32 patients received fenoldopam and 32 patients received dopamine. Fenoldopam (Corlopam, Elan Pharma Italia S.p.A, now Cephalon Frazer, PA, USA) was supplied as a sterile, lyophilized powder in vials containing 25 mg, reconstituted with bacteriostatic water for intravenous injection. Dopamine (Revivan, Astrazeneca SPA, Palazzo Volta, V F Sforza, Basiglio, Milan) was supplied as a sterile solution in 5 ml vials containing 200 mg, diluted with bacteriostatic water for intravenous injection. These solutions were both administered by continuous infusion through a central venous catheter. Fenoldopam dosage was 0.05 mcg/kg/min and dopamine dosage was 2.5 mcg/kg/min. Drug administration started after anesthesia induction and lasted 12 hours after surgery. Study drugs were not distinguishable from each other.

Patients received standard monitoring and anesthesia. Heart rate and blood pressure were recorded at baseline, 5 minutes after induction of anesthesia, 30 minutes after starting the study drug, at the end of surgery and before leaving the theatre. Intraoperative and 24 hours urinary output were measured. Use of diuretics and the occurrence of hypotensive episodes requiring vasoconstrictors were recorded as well.

We tested the hypothesis that the intravenous administration of fenoldopam reduces the incidence of postoperative ARF as compared to intravenous dopamine. The primary endpoint was the incidence of ARF following surgery, defined as a postoperative increase in serum creatinine of 25% or more. (11,12) Serum creatinine was measured during the preoperative period, at the end of surgery and every day during the patients' hospitalization. Loop diuretics were administered early in the course of ARF to convert an oliguric to a non oliguric state.

On the basis of previous data investigating postoperative ARF in high-risk patients we anticipated a 40% frequency of ARF in the standard treatment group and assumed a 10% incidence of ARF after treatment with fenoldopam. Using a statistical significance level (alpha) of 0.05 and a power of 80% we calculated that we would need a sample size of 32 patients per group. Therefore, the total study population was $2 * 32 = 64$ patients.

All data were analyzed according to the intention-to-treat principle. Data were stored electronically and analyzed by use of Epi Info 2002 software (CDC) and SAS software, version 8 (SAS Institute). All data analysis was carried out according to a pre-established analysis plan. Dichotomous data were compared by using two-tailed Chi square test with the Yates correction or Fisher's exact test when appropriate. Continuous measures were compared by analysis of variance (ANOVA) or the Mann-Whitney U test when appropriate. Two sided significance tests were used throughout.

Results

Patients receiving fenoldopam or dopamine showed a similar incidence of postoperative ARF: 11/32 (34%) in the fenoldopam group vs 14/32 (44%) in the dopamine group ($p=0.6$). No renal replacement therapy and no deaths were observed in this population.

Baseline demographic and clinical characteristics are reported in table 1. All participants who underwent random allocation were analyzed according to group assignment.

Table 2 shows the intraoperative data in the two study arms with no difference between groups in urinary output, heart rate, arterial pressure and use of vasoconstrictors. Table 3 shows postoperative data with no difference in the incidence of ARF between the two groups (patients receiving fenoldopam versus patients receiving dopamine), irrespective of definition used: 25% creatinine increase (34% versus 44% $p=0.6$); 50% creatinine increase (12% versus 22%$p=0.5$); 100% creatinine increase (3% versus 9% $p=0.3$).

In the overall population serum creatinine raised from a baseline level of

114±53 μmol/l to a postoperative peak of 158+13 μmol/l (p=0.008), while in the patients who developed ARF it showed a 85% increase, from 114+55 μmol/l to 211±185 μmol/l (p=0.01).

Discussion

The principal finding of this prospective, randomized, double-blinded trial is that a 0.05 mcg/kg/min dose of fenoldopam, lasting 12 hours, does not reduce the risk of perioperative acute renal failure when compared to dopamine.

Our results are in accordance with only two previous reports in which fenoldopam was used at a low dosage (9) or for a short period of time. (10) All the other studies (7,8,13-20) and meta-analyses (5,6) investigating fenoldopam's effects on renal function showed positive results. In most of them fenoldopam was administered at a higher dosage (at least 0.1 mcg/kg/min) or for at least 24 hours.

Oliver et al. (10) compared the hemodynamic and renal effects of fenoldopam in patients who underwent abdominal aortic surgery requiring cross clamping of the aorta with another therapeutic option (dopamine or sodium nitroprusside). The number of patients who experienced an increase in their serum creatinine of 44 μmol/l at 1h, 24 h and 4–8 days after their arrival in intensive care unit did not differ between fenoldopam (0/28, 0/28, 0/24) and controls (0/27,1/28, 1/20). The major limitation of this study was that the administration of fenoldopam was restricted to the intraoperative period.

In the study of Bove et al. (9) fenoldopam mesylate did not prevent ARF in a high-risk population of patients undergoing cardiac surgery. ARF, defined as a postoperative serum creatinine level increase of 25% or more, developed in 42.5% of patients treated with fenoldopam versus 40% of patients treated with dopamine. Even using a restricted definition of ARF (50% serum creatinine increase), this complication developed in 25% of patients in both groups.

Fenoldopam mesylate is a unique vasodilator that selectively increases both renal cortical and outer medullary blood flow while decreasing systemic vascular resistance. (3) Fenoldopam has been shown to increase renal blood flow in patients with and without chronic renal insufficiency (21) but there is, at present, no clear data from prospective clinical trials to support a reduction in the incidence of ARF. Beneficial renal effects have been demonstrated at an infusion rate of 0.03 mcg/kg/min, far below the dosages usually required to lower systemic blood pressure. (21)

Fenoldopam has demonstrated nephroprotective properties in critically ill patients and in patients undergoing major surgery. A meta-analysis (5) of 16 randomized clinical trials (RCTs) including 1290 patients (622 receiving fenoldopam and 668 placebo or the best available treatment, mostly low dose dopamine) was recently performed including 5 trials in cardiac surgery, 3 in vascular surgery, 2 in liver surgery, 1 in renal transplants and 5 in ICU (intensive care unit). Overall analysis showed that, in comparison to the best available treatment, the use of fenoldopam reduced the risk of renal replacement therapy (34/525 [6.5%] in the fenoldopam group vs. 59/569 [10.4%] in the control arm, OR=0.54 [0.34-0.84], p for effect=0.007, p for heterogeneity=0.92, I^2=0%), and all-cause mortality (81/537 [15.1%] vs. 110/581 [18.9%], OR=0.64 [0.45-0.91], p for effect=0.01, p for heterogeneity=0.92, I^2=0%), as well as AKI (84/525 [16.0%] vs. 161/569 [28.3%], OR=0.43 [0.32-0.59], p for effect <0.001, p for heterogeneity=0.09, I^2=41%).

In a second meta-analysis (6) fenoldopam was confirmed to reduce mortality and the need for renal replacement therapy in the setting of cardiovascular surgery. Thirteen clinical studies that included 1059 patients (528 received fenoldopam and 531 placebo or the best available treatment) were considered and suggested that fenoldopam usage reduced the risk of renal replacement therapy (30/528 [5.7%] in the fenoldopam group vs. 71/531 [13.4%] in the control arm (OR=0.37 [0.23-0.59], p for effect <0.001, p for heterogeneity = 0.51, I^2 = 0%, number needed to treat = 13) and of in-hospital death (28/501 [5.6%] in the fenoldopam group vs. 55/503 [10.9%] in the control arm (OR=0.46 [0.29-0.75], p for effect = 0.02, p for heterogeneity = 0.66, I^2 = 0%, number needed to treat = 19).

Few authors (10,21) performed randomized trials using fenoldopam in a non-transplant or non-cardiosurgical setting.

Halpenny et al. reported their experience with patients undergoing elective aortic surgery requiring infrarenal aortic cross-clamping. (19) They randomized 27 patients to receive either fenoldopam 0.1 mcg/kg/min (14 patients) or placebo (13 patients) prior to surgical skin incision until release of the aortic clamp and evidenced that serum creatinine concentration increased significantly from baseline on the first postoperative day in the placebo group but not in the fenoldopam group, with no hemodynamic instability.

We acknowledge that, compared to other studies, we examined a shorter time of infusion of the drug (12 hours). The studies that showed the largest benefits used fenoldopam for more than 48 hours. (20) Furthermore we compared fenoldopam to dopamine and not to a placebo. Dopamine was the standard treatment for patients at high risk of developing ARF in our center and we considered dopamine to be the best available treatment. Even if there is no evidence on the benefits of low dose dopamine in preventing renal damage, it is "at least not harmful" if used for a limited period of time as stated by recent review articles (22) and meta-analysis. (23) A notable finding of a recent meta-analysis (23) was that dopamine does not appear to increase the risk of death, ARF or hemodialysis. Indeed, dopamine seems to be a relatively safe agent, although totally ineffective for preventing or treating renal dysfunction. The incidence of ARF in this population was modest: this could help to explain the differences in results obtained in the present study from those reported

earlier. Interestingly, fenoldopam is still widely studied. (24-28)

Conclusion

Based on the current study, fenoldopam should not be used at this dosage and for this length of time as a prophylactic measure to prevent ARF in a surgical population. The authors acknowledge that fenoldopam may be beneficial in other subgroups or if a larger population is studied or, most important, if longer infusion times and higher doses of fenoldopam are administered.

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