Fenoldopam Reduces the Need for Renal Replacement Therapy and In-Hospital Death in Cardiovascular Surgery: A Meta-Analysis

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Objective: **Acute renal failure is a common and threatening complication in patients undergoing cardiovascular surgery. To determine the efficacy of fenoldopam in the prevention of acute renal failure, the authors performed a systematic review of randomized, controlled trials and propensity-matched studies in patients undergoing cardiovascular surgery.**

Design: **Meta-analysis.**

Setting: **Hospitals.**

Participants: **A total of 1,059 patients from 13 randomized and case-matched studies were included in the analysis.**

Interventions: **None.**

Measurements and Main Results: **Google Scholar, PubMed, and scientific sessions were searched (updated November 2006). Authors and external experts were contacted. Four unblinded reviewers selected controlled trials that used fenoldopam in the prevention or treatment of acute renal failure in cardiovascular surgery. Four reviewers independently abstracted patient data, treatment characteristics, and outcomes. Pooled estimates showed that fenoldopam consistently and significantly reduced the need for renal replacement therapy (odds ratio = 0.37 [0.23-0.59], $p < 0.001$) and in-hospital death (odds ratio = 0.46 [0.29-0.75], $p = 0.01$). These benefits were associated with shorter intensive care unit stay (weighted mean difference [WMD] = −0.93 days [−1.27; −0.58], $p = 0.002$). Sensitivity analyses, tests for small study bias, and heterogeneity assessment further confirmed the main analysis.**

Conclusions: **This meta-analysis provides evidence that fenoldopam may confer significant benefits in preventing renal replacement therapy and reducing mortality in patients undergoing cardiovascular surgery.**

KEY WORDS: fenoldopam, cardiac surgery, vascular surgery, kidney, meta-analysis, diuretics, mortality, renal replacement therapy, acute renal failure

AMONG THE MOST serious complications of cardiovascular surgery, acute renal failure (ARF) stands out as one of the least predictable and preventable. Indeed, its incidence varies between 1% and 30%, and, despite improvements in intensive care medicine and the delivery of renal replacement therapy (RRT), the mortality associated with ARF remains unacceptably high.[1]

The observation that renal blood flow decreases after the onset of ARF[2] has led to numerous clinical trials investigating the efficacy of parenteral vasodilators in reducing progression to RRT and improving patient survival. Fenoldopam is a selective dopamine receptor-1 agonist that causes DA-1 receptor–mediated vasodilatation. It selectively increases both renal cortical and outer medullary blood flow.[3]

Controlled clinical studies showing the clinical efficacy of fenoldopam in cardiovascular surgery are limited by small sample sizes. Numerous positive but underpowered reports have appeared in the literature, whereas trials showing no benefit exist.[4-24]

Fenoldopam has recently shown nephroprotective properties in critically ill patients or those undergoing major surgery,[25] but this article did not include some very recent randomized studies[7,15,16] and case-matched studies[6,18,20] and thus had no power to draw definitive conclusions in the specific setting of cardiovascular surgery.

Because no single prospective study and no meta-analysis support a protective effect of fenoldopam on reducing the incidence of RRT in patients undergoing cardiovascular procedures, the authors conducted a meta-analysis of 13 clinical studies comparing fenoldopam with placebo or usual care.

METHODS

The authors attempted to identify all published and unpublished studies of fenoldopam in cardiovascular surgery using Google Scholar and PubMed (updated November 30, 2006). Pertinent studies were independently searched by 4 trained investigators (G.L., G.G.L.B.-Z., G.M., and O.F.). The full PubMed search strategy, including as key words fenoldopam, kidney disease, renal failure, and cardiac surgery, was developed according to Biondi-Zoccai et al[26] and is available in the appendix. Further hand or computerized searches involved the recent (2002-2006) conference proceedings from the International Anesthesia Research Society, American Heart Association, American College of Cardiology, American Society of Anesthesiologists, and European Society of Cardiology congresses. In addition, the authors used backward snowballing (ie, scanning of reference of retrieved articles and pertinent reviews) and contacted international experts for further studies. No language restriction was enforced, and non–English-language articles were translated before further analysis.

References obtained from database and literature searches were first independently examined at the title/abstract level by 4 investigators (G.L., G.G.L.B.-Z., G.M., and O.F.), with divergences resolved by consensus and then, if potentially pertinent, retrieved as complete articles. The following inclusion criteria were used for potentially relevant studies: (1) clinical trial comparing fenoldopam with control

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treatment, (2) clinical trial using random allocation or adjustment for covariates (for nonrandomized studies), and (3) clinical trial in patients undergoing cardiovascular surgery. The exclusion criteria were (1) nonparallel design (ie, crossover) randomized trials, (2) duplicate publications (in this case only the article reporting the longest follow-up was abstracted), (3) nonhuman experimental studies, and (4) no outcome data as far as RRT or death are concerned. The 4 investigators selected studies for the final analysis by independently assessing compliance to selection criteria. Divergences from the selection criteria were resolved by consensus.

The 4 investigators independently extracted data on study design (including patient selection and treatment allocation), population, clinical setting, fenoldopam dosage, treatment duration (Table 1), additional treatments, and requirements for RRT with divergences resolved by consensus. If the required data could not be extracted from the published report, at least 2 separate attempts at contacting original authors were made.

The primary endpoint of the authors' analysis was to determine the effect of fenoldopam on the number of patients requiring at least 1 episode of RRT. The coprimary endpoint was the incidence of in-hospital mortality. Secondary endpoints included peak serum creatinine levels, and the duration of mechanical ventilation, intensive care unit and hospital stay, hypotension, or the use of vasoconstrictors.

The internal validity of included trials was appraised according to The Cochrane Collaboration methods (ie, judging the risk for selection, performance, attrition, and adjudication biases) and expressed as low risk of bias (A), moderate risk of bias (B), high risk of bias (C), or incomplete reporting leading to the inability to ascertain the underlying risk of bias (D).[27] In addition, allocation concealment was explicitly distinguished as adequate (A), unclear (B), inadequate (C), or not used (D) (Table 2). Two independent reviewers (G.L. and G.G.L.B.-Z.) appraised the study quality, with divergences resolved by consensus.

Binary outcomes from individual studies were analyzed according to the Mantel-Haenszel model to compute individual odds ratios (ORs) with pertinent 95% confidence intervals (CI), and a pooled summary effect estimate was calculated by means of a fixed-effects model. Weighted means differences (WMDs) and 95% CIs were computed for continuous variables.[27] The authors compared the robustness of findings from the primary analysis to the effects of study population and baseline risk for any of the primary outcomes through a series of sensitivity analyses, including random-effects model, and by withdrawing 1 study at a time.

Statistical heterogeneity and inconsistency were measured by using, respectively, Cochrane Q tests and I^2.[28] The risk of small study bias (including publication bias) was assessed by visual inspection of the funnel plots.[29] Statistical significance was set at the 2-tailed 0.05 level for hypothesis testing and at 0.10 for heterogeneity testing. According to Higgins and Green,[2] I^2 values around 25%, 50%, and 75% were considered representing, respectively, low, moderate, and severe statistical inconsistency. Unadjusted p values are reported throughout. Computations were performed with SPSS 11.0 (SPSS Inc, Chicago, IL) and RevMan 4.2 (freeware available from The Cochrane Collaboration).[27]

RESULTS

Database searches, snowballing, and contacts with experts yielded a total of 197 citations (Fig 1). Once 175 nonpertinent titles or abstracts were excluded, the authors retrieved in complete form and assessed according to the selection criteria 22 studies. A further 9 studies were excluded because of nonexperimental design[30] and because no outcome data (RRT and/or death) were reported.[8-10,11,13,14,21,24] The authors finally identi-

Table 1. Description of Studies Included in the Systematic Review

Author	Journal	Design	N	Publication	Setting	Control Group	Dose (μg/kg/min)	Duration of Treatment (hours)	Baseline Serum Creatinine (mg/dL) (mean ± SD)
Bove (2005)	Circulation	Randomized	80	Full paper	Cardiac surgery	Dopamine	0.05	24	1.56 ± 0.78 *v* 1.54 ± 0.59
Caimmi (2003)	J Cardiothorac Vasc Anesth	Randomized	160	Full paper	Cardiac surgery	Dopamine or dobutamine after furosemide	0.1-0.3	24	1.82 ± 0.2 *v* 1.78 ± 0.3
Cicchetti (2004)	Minerva anestesiol	Case matched	20	Abstract	Vascular surgery		0.03		
Cogliati (in press)	J Cardiothorac Vasc Anesth	Randomized	193	Full paper	Cardiac surgery	Placebo	0.10	24	1.8 ± 0.4 *v* 1.9 ± 0.3
Halpenny (2002)	Eur J Anaesthesiol	Randomized	27	Full paper	Vascular surgery	Placebo	0.10	2	1.12 ± 0.19 *v* 0.98 ± 0.14
Martinelli (2006)	Minerva anestesiol	Randomized	30	Abstract	Cardiac surgery	Standard treatment	0.09	72	2.05 ± 0.6 *v* 1.70 ± 0.2
Oliver (2006)	Anesth Analg	Randomized	59	Full paper	Vascular surgery	Dopamine ± nitroprusside	>0.05	4	1.2 ± 0.3 *v* 1.3 ± 0.2
Pittarello (2003)	Minerva anestesiol	Randomized	24	Abstract	Cardiac surgery	Placebo	0.05	48	2.53 ± 1.79 *v* 1.56 ± 0.15
Ranucci (2004)	Ann Thorac Surg	Propensity matched	216	Full paper	Cardiac surgery	Standard treatment	0.08	24	2.46 ± 0.85 *v* 2.44 ± 0.85
Renzini (2004)	Minerva anestesiol	Randomized	30	Abstract	Cardiac surgery	Placebo	0.03-0.1	48	1.50 ± 0.2 *v* 1.51 ± 0.3
Roasio (in press)	J Cardiothorac Vasc Anesth	Case matched	92	Full paper	Cardiac surgery	Standard treatment	0.10	48	2.3 ± 0.68 *v* 2.0 ± 0.66
Sheinbaum (2003)	Rev Cardiovasc Med	Case matched	58	Full paper	Vascular surgery		0.05	24	
Tumlin (2005)	AJKD	Randomized	70	Full paper (subgroup)	Cardiac surgery	Placebo	0.05-0.3	72	1.3 ± 1.23 *v* 1.3 ± 0.53

Abbreviation: N, number of patients included in each study.