Fenoldopam in newborn patients undergoing cardiopulmonary bypass: controlled clinical trial

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Abstract

We determined if low dose fenoldopam in neonates already receiving conventional diuretics improves urine output, fluid balance, acute kidney injury incidence (AKI) and time to extubation. A prospective controlled clinical trial in a pediatric cardiac intensive care unit on 40 neonates undergoing cardiac surgery with cardiopulmonary bypass, excluding simple ventricular septal defect and atrial septal defect. Fenoldopam was infused at a low dose of 0.1 μg/kg/min soon after anesthesia induction and infusion prolonged for 72 h in 20 patients. Twenty neonates with standardized perioperative therapy except fenoldopam administration served as controls. Demographic, hemodynamic, daily urine output, creatinine, creatinine clearance, serum and urinary sodium and potassium were recorded. Inotropic score (IS) was calculated as a surrogate for the degree of hemodynamic impairment. Low dose fenoldopam infusion did not show beneficial effects in renal function. The treatment did not significantly affect IS value, AKI incidence, fluid balance control, time to sternal closure, time to extubation and time to intensive care unit discharge. Low dose fenoldopam in neonates undergoing cardiac surgery with CPB did not produce effects on urine output, fluid balance and AKI incidence. Fenoldopam was well tolerated and did not negatively affect hemodynamics and vasopressor support.

Keywords: Fenoldopam; Acute kidney injury; Cardiopulmonary bypass; Congenital heart disease

1. Introduction

Substantial fluid retention and tissue edema after cardiac surgery with cardiopulmonary bypass (CPB) in neonates are commonly associated with a prolonged intensive care unit (ICU) stay and adverse outcome. The pathogenesis of this condition is multifactorial and is related to neurohumoral and inflammatory responses to CPB, acute kidney injury (AKI), the need for a high input volume (drugs, parenteral nutrition, red packed blood cells, fresh frozen plasma), low cardiac output syndrome, residual heart defects or sepsis. In more than 3.5% of children after open heart surgery the cascade of reactions triggered by CPB leads to systemic inflammatory response syndrome, capillary leak syndrome, AKI and eventually multi-organ failure [1]. In these patients high dose loop diuretics are routinely administered aiming to avoid oliguria and eventually enhance diuresis; in some centers, peritoneal dialysis (PD) is delivered in order to achieve a negative fluid balance. Fenoldopam, a selective dopamine A1 receptor agonist, causes systemic vasodilatation and increased renal blood flow, increases renal corticomedullary perfusion, renal corticomedullary oxygenation, and glomerular filtration rate, and may thus act as a diuretic and nephroprotective agent. It has recently been advocated as an antinflammatory agent [2]. This drug was initially used in adults for short-term treatment of severe hypertension [3]. However, recently, fenoldopam has been extensively utilized in critically ill patients at risk or with established AKI. A systematic review of randomized controlled trials of intensive care unit patients or those undergoing major surgery concluded that fenoldopam reduces the need for renal replacement and mortality in patients with AKI [4]. In a retrospective study, Costello and coworkers evaluated the effects of fenoldopam administration to a cohort of pediatric patients requiring cardiac surgery with CPB: they found that fenoldopam improved urine output in neonates who were failing to achieve an adequate negative fluid balance despite conventional diuretic therapy after cardiac surgery and CPB [5].

The objective of this study was to prospectively confirm these findings and to determine if low dose fenoldopam in neonates already receiving conventional diuretics could help to achieve higher urine output, more negative fluid balance, to reduce AKI incidence and time to extubation.

2. Materials and methods

A prospective, non-blinded, controlled clinical trial was conducted on 40 neonates undergoing major cardiac surgery.
requiring CPB. In order to obtain two comparable populations, cases and controls were assigned in equal parts to one of the following groups: biventricular cardiac anatomy requiring CPB without deep hypothermic circulatory arrest (DHCA), univentricular cardiac anatomy requiring CPB without DHCA, biventricular cardiac anatomy requiring CPB with DHCA, univentricular cardiac anatomy requiring CPB with DHCA (Table 1). A case and a control of each group were alternatively and consecutively enrolled: even if a randomization protocol was absent, authors were not aware of which patient would have received fenoldopam or served as a control before enrollment. No violations to this scheme occurred. Exclusion criteria were: age over 30 days, surgery without scheduled need for CPB, need for previous non-cardiac surgery. Patients affected by simple ventricular septal defect and atrial septal defect were also excluded. Risk Adjusted classification for Congenital Heart Surgery (RACHS-1) was utilized to compare the severity of surgical risk in the populations [6].

Fenoldopam was infused at 0.1 μg/kg/min soon after anesthesia induction and infusion was prolonged for 72 h. Infusion had to be interrupted in case of severe hypotension (systolic arterial pressure below 40 mmHg) refractory to maximal vasopressors increase. The remaining therapy was unchanged in both groups according to the institutional protocol: milrinone 0.75 μg/kg/min, dopamine up to 15 μg/kg/min and eventually epinephrine up to 0.2 μg/kg/min were started at weaning from CPB in order to achieve a systolic pressure over 60 mmHg. A continuous infusion of fenoldopam was started at weaning from CPB in order to achieve a maximal vasopressors increase. The remaining therapy was also unchanged in both groups.

Table 1
Classification of patients treated with fenoldopam and controls. All neonates underwent cardiopulmonary bypass

<table>
<thead>
<tr>
<th>Fenoldopam group</th>
<th>Controls</th>
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<tbody>
<tr>
<td>Number/diagnosis/surgery</td>
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</tr>
<tr>
<td>Univentricular anatomy</td>
<td>5/PA-IS/OP-BT shunt</td>
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DHCA, deep hypothermic circulatory arrest; PA-IS, pulmonary atresia with intact septum; OP-BT shunt, outflow patch and Blalock Taussig shunt; TOF, tetralogy of Fallot; TGA, transposition of the great arteries; VSD, ventricular septal defect; HLHS, hypoplastic left heart syndrome; IAO, interrupted aortic arch; AAH, aortic arch hypoplasia.

The primary outcome was the daily urine output difference in the fenoldopam group vs. controls. Secondary outcomes were fluid balance control, difference in IS value, AKI/ID incidence, time to sternal closure, time to extubation and time to ICU discharge in the two groups. The Ethics Committee of Bambino Gesù Hospital had approved the protocol. Written informed consent was obtained from each subject’s parent or guardian.

2.1. Statistical analysis

Intention to treat was applied and all enrolled patients were considered for statistical analysis at the end of the study. All data are expressed as median (interquartile range). Mann-Whitney non-parametric test was utilized in order to compare differences in anagraphic parameters (age, weight) and baseline characteristics at anesthesia induction (RACHS-1, creatinine value, systolic arterial pressure, CPB time, DHCA time, cross-clamp time) between the two groups. χ²-test was utilized to compare difference in patients’ sex, AKI/ID incidence, delay in sternal closure and ICU discharge. Two-way analysis of variance was utilized to evaluate differences in urine output, fluid balance, creatinine, creatinine clearance, systolic arterial pressure, heart rate, IS within the two groups during the first three postoperative days. A P-value <0.05 was considered significant. Our study had an 80% power to detect an average difference between groups of 1.75 ml/kg/h of urine output with a significance level (alpha) of 0.05 (two-tailed). Statistical analysis was performed with the GraphPad Prism 4.0 software package (GraphPad Software, San Diego, CA, USA).

3. Results

The two groups (20 patients treated with fenoldopam and 20 controls) had similar demographic and baseline characteristics (Table 2). All patients received furosemide continuous infusion at a dosage of 10 mg/kg/day during the examined period. We found that serum creatinine levels and creatinine clearance were not significantly different between the two groups in the three days (Fig. 1). No changes were found after the 72-h period in serum and urinary sodium and potassium concentrations in both groups (Table 3). Urine output and fluid balance analysis did not

Table 2
Number of patients and characteristics at anesthesia induction and surgery

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show significant differences between groups (P: 0.064). Nonetheless, the fenoldopam group showed to have a non-significant urine output increase compared to controls (Fig. 2). The fenoldopam group tended to achieve a more negative fluid balance in the postoperative day 1 and 2 and in controls in day 3 (Fig. 3; P: 0.055). Fenoldopam infusion was never interrupted for hypotension and all treated patients concluded the 72 h without any other reported...
side effect. Systolic pressure, heart rate and central venous pressure did not show any significant difference between the two groups (Table 3). The need for inotropes and vasopressors, as shown by median IS in the examined time period, was similar between the two groups (Table 3). Median lactate levels did not significantly differ in the two groups and showed a similar trend to progressive decrease from ICU admission to the third examined day (P: 0.056) (Table 3). Sternal closure was delayed in 13 (65%) fenoldopam and 9 (45%) control patients. Sternal closure time was 2 days (2–4) in fenoldopam group vs. 2 days (2–2.5) in controls. Treated patients were extubated on day 4 (3–6.5) vs. day 4 (3–5.5) on controls. AKI occurred in five patients (25%) in the fenoldopam group and 6 (30%) among controls. Patients were discharged from ICU on the 7th day (4–10) in the fenoldopam group and on the 7th day (5.5–10) in the control group. Only one patient in the control group died before ICU discharge.

4. Discussion

In our small cohort of post CPB neonates, low dose fenoldopam infusion did not show beneficial effects in urine output. Fenoldopam did not significantly affect any of the secondary outcomes (IS value, AKI incidence, fluid balance control, time to sternal closure, time to extubation and time to ICU discharge). A slight trend to a higher urine output and a more negative fluid balance early after surgery could be observed. Fenoldopam did not cause any side effect and drug related tachycardia or hypotension. The rationale for using this agent in such a trial came from experimental and adult clinical studies. Fenoldopam selectively binds to dopamine DA1 receptors on smooth muscle cells of renal and splanchnic vascular beds. Activation of these receptors increases intracellular cyclic adenosine monophosphate (cAMP)-dependent protein kinase A activity, enhancing relaxation of vascular smooth muscle [9]. In the kidneys, increased concentration of cAMP in the proximal tubules and medullary portion of the ascending loop of Henle inhibits the sodium-potassium adenosine triphosphatase pump and the sodium-hydrogen exchanger. Fenoldopam infusion blunts aldosterone production and results in increased renal blood flow, urinary sodium excretion, and urine output. Fenoldopam is rapidly titratable, with an elimination half-life of about 10 min [10].

Low dose fenoldopam (0.1 μg/kg/min) was selected for this pilot experience because this was the first prospective study in children and we tried to avoid any possible hemodynamic side effect. However, many previous studies in adults administered similar dosages with positive results [11]. Furthermore, since drug administration started before CPB as a pre-emptive measure to improve renal function we considered that the lowest dosage might have been adequate. A prospective single-center, randomized, double-blind trial was recently performed in 80 adult patients undergoing high risk cardiac surgery: fenoldopam was infused at a dosage of 0.05 μg/kg/min and compared with 2.5 μg/kg/min of dopamine. As clearly stated by the authors, the only difference within the two groups was noted in the development of hypotension and higher use of norepinephrine during CPB in the fenoldopam group [12].

Pediatric experience in the ICU is substantially limited to some case series [13, 14] and to a retrospective study by Costello and coworkers in post cardiac surgery neonates [5]. These authors started fenoldopam administration a median of six days after surgery using an initial median dose of 0.1 μg/kg/h but titrated the drug to a maximum dose of median 0.3 μg/kg/h (range 0.1–1). Relative resistance to stimulation of DA1 receptors in neonatal kidneys is related to ontogenic differences in receptor density, affinity, coupling to intracellular second messengers or more distal mechanisms [15]: these receptors might require high fenoldopam doses to achieve significant clinical effects. Nonetheless, we considered that the preliminary experience from Costello, given its retrospective design, could not be taken as a reliable report in order to design a prospective study with similar drug doses. Furthermore, these authors compared patients urine output before and after fenoldopam infusion: the median baseline value of that cohort and the increase they obtained were similar to the one we observed in both examined groups during the three study days. A recent retrospective review on fenoldopam administration to 13 critically ill children, included five patients who received fenoldopam in order to optimize renal blood flow as postoperative renal prophylaxis: urine output change was not significant in this small subgroup [16].

However, we also analyzed daily fluid balance in our patients and noticed a different trend between groups: fenoldopam patients resulted to have a more negative fluid balance in the first 48 h with respect to controls, maybe because they tended to require less fluid intake than controls. AKI/PD incidence seemed not to be affected by this drug. Further studies are required to determine if larger doses are beneficial in neonates undergoing cardiac surgery.

Our study had some important limitations: first, the lack of a placebo controlled randomized design and thus the internal validity of the study may have been compromised by treatment assignment, assessment and management bias. Randomization, however, was warranted by the alternative enrollment of patients in one of the two groups: patient name and group assignment was unknown by the researchers until the induction phase was completed in order to avoid selection bias. Furthermore, the sample size was small and our study may have been under powered to detect smaller differences in urine output between treatment groups. Considering urine output standard deviation...
of our control group on postoperative day 1, a randomized clinical trial based on urine output as the primary outcome should require a sample size of 150 patients per group, in order to detect a difference in urine output of 0.8 ml/kg/h with statistical power of 80% and a significance level (alpha) of 0.05. Nevertheless, this was a pilot trial and we tried to enroll very similar groups: a larger multicenter randomized controlled study is needed to reach such a sample size and to draw definitive conclusions.

5. Conclusion

Low dose fenoldopam in neonates undergoing cardiac surgery with CPB did not produce differences in urine output, fluid balance and AKI incidence. Fenoldopam was well tolerated and did not negatively affect hemodynamics and vasopressor support. Further larger randomized controlled studies using higher drug doses are warranted.

References