Beneficial effect of fenoldopam mesylate in preventing peak blood lactate level during cardiopulmonary bypass for paediatric cardiac surgery

Laura Ressia, Maria Grazia Calevo, Franco Lerzo, Anna Maria Carleo, Lara Petrucci and Giovanni Montobbio

Department of Anaesthesia and Intensive Care Medicine, Istituto Giannina Gaslini, Genoa, Italy
UOSD Epidemiology, Biostatistics and Committees, Istituto Giannina Gaslini, Genoa, Italy

* Corresponding author. UOSD Epidemiology, Biostatistics and Committees, Istituto Giannina Gaslini, Largo Gerolamo Gaslini 5, 16148 Genoa, Italy.
Tel: +39-010-5636301/423; fax: +39-010-8981116; e-mail: mariagraziacalevo@ospedale-gaslini.ge.it (M.G. Calevo).

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Abstract

OBJECTIVES: To evaluate the efficacy of fenoldopam mesylate (dose 0.2 µg/kg/min) in reducing the occurrence of hyperlactataemia (i.e. peak level of blood lactate >2.0 mM/l) during cardiopulmonary bypass (CPB) in paediatric cardiac surgery. Hyperlactataemia occurring during CPB for paediatric cardiac surgery is considered an early biomarker of an increased risk of poor outcome.

METHODS: This was a dose/effectiveness clinical study applying Simon's two-stage optimal design with 5% type I error rate and 90% statistical power. Following parents' written informed consent, 53 children undergoing elective cardiac surgery with CPB between March 2009 and February 2012 were enrolled. Inclusion criteria were children weighing 3–15 kg scheduled for elective cardiac surgery and with expected CPB time of 60–180 min. Patients requiring surgery with total circulatory arrest were excluded. All patients received fenoldopam infusion at a dose of 0.2 µg/kg/min from the beginning of surgery until the end of CPB.

RESULTS: The primary end-point was the evaluation of response to fenoldopam, i.e., blood lactate levels ≤2.0 mM/l. A total of 53 children, median age 5.7 months (range 11 days to 48 months) were enrolled. In the first stage, 18 of 19 (95%) children achieved normalization of lactate values. Then the study was continued to stage II by enrolling an additional 34 patients. At study conclusion, 96.2% of patients showed normalized lactate values. Fenoldopam infusion was well tolerated in all patients. No adverse events were observed.

CONCLUSIONS: In this study, fenoldopam at a dose of 0.2 µg/kg/min was well tolerated in paediatric patients undergoing elective cardiac surgery with CPB. In 96.2% of patients, infusion of fenoldopam was associated with intraoperative blood lactate <2.0 mM/l.

Keywords: Fenoldopam mesylate • Cardiopulmonary bypass • Paediatric cardiac surgery • Blood lactate • Splanchnic perfusion • Hyperlactataemia

INTRODUCTION

Hyperlactataemia occurring during cardiopulmonary bypass (CPB) for paediatric cardiac surgery is considered an early marker of an increased risk of poor outcome [1, 2] even in low- and medium-risk procedures [3].

While hyperlactataemia associated with other signs of hypoperfusion and haemodynamic instability is a clear expression of anaerobic metabolism [4], it is more difficult to explain the increase in blood lactate levels observed in many non-complicated low- and medium-risk patients undergoing paediatric cardiac surgery. Some authors [5, 6] consider hyperlactataemia is not associated with signs of hypoperfusion as a marker of regional hypoxia and splanchnic hypoperfusion, even without the appearance of clinical signs of organ dysfunction. Some studies in adults evaluating mucosal acidosis by means of gastric tonometry suggested that the gut is one of the first organ systems undergoing ischaemic injury at the time of haemodynamic stress [7, 8].

Fenoldopam mesylate is a highly selective agonist of the peripheral dopamine receptor (DA1). It is well known for its renal protective properties [9–12], and it has been shown to increase splanchnic perfusion through DA1-mediated vasodilatation [9].

Fenoldopam is not labelled for paediatric use and limited information is available about its pharmacodynamics and pharmacokinetics in children.

Our aim was to investigate whether, in the paediatric population, fenoldopam could reduce the occurrence of hyperlactataemia during CPB by means of improved perfusion.

To the best of our knowledge, this is the first clinical study evaluating the influence of fenoldopam on blood lactate levels in a paediatric population during CPB for paediatric cardiac surgery.
METHODS

The study population included 53 children undergoing elective cardiac surgery with CPB between March 2009 and February 2012 at our paediatric hospital.

Inclusion criteria were the following: children weighing 3–15 kg undergoing elective cardiac surgery and with an expected CPB time between 60 and 180 min. Patients requiring surgery with total circulatory arrest were excluded as well as patients with preoperative inotrope infusion and patients who had severe hypotension on induction of anaesthesia.

The study was approved by our Institutional Ethics Committee on 11 February 2009 (Ethics Committee No. 2009-009115-22). Written informed consent was obtained from all parents of children before enrolment. The study was undertaken in accordance with the declaration of Helsinki (2009).

In all patients, anaesthesia was administered according to our institutional protocol. Anaesthesia was induced with intravenous midazolam and carried out by means of high-dose opioids (fentanyl 50 µg/kg) supplemented with midazolam and rocuronium.

Our standard haemodynamic monitoring included measurement of arterial pressure, central venous pressure, nasopharyngeal, oesophageal and rectal temperatures, and urine output. CPB was performed by means of cannulation of the ascending aorta and double venous cannulation of the superior and inferior vena cava. CPB was initiated with the use of a bolus of 3 mg/kg of unfractionated heparin to reach and maintain an activated clotting time >450 s. The CPB circuit consisted of a hollow fibre oxygenator with an arterial filter and a centrifugal pump.

In all children, the CPB circuit was primed with a solution containing red blood cells, plasma and 4% albumin solution titrated to reach a haematocrit value of 34%. All procedures were performed by using a regimen of mild hypothermia (32–34°C). Blood flow rate was set following our institutional protocol and adjusted based on haemodynamic parameters. During CPB, we monitored continuously central venous saturation (ScVO2) values by means of oximetric cells placed inside the venous line of the CPB circuit (Biotrend Medtronic). At the end of CPB, heparin was reversed with protamine sulphate and red blood cells were transfused when necessary to reach a target ScVO2 >65%.

All patients received fenoldopam infusion at the low dose of 0.2 µg/kg/min from the beginning of surgery until the end of CPB. In the literature [13], higher doses were used to achieve a hypotensive effect. In our experience, the selected dose was rarely associated with haemodynamic side effects, which could be harmful in small children with congenital cardiopathy.

The following data were collected: (i) preoperative data including demographic information, preoperative conditions, associated diseases, type and complexity of the operation according to Aristotle score [14]; (ii) intraoperative data, including haemotocrit, CPB and aortic cross-clamping duration, ScVO2 values, near infrared spectroscopy (NIRS) values (INVOS™ 5100 C cerebral/somatic oximeter).

Lactate values were obtained from arterial blood gas analysis. The peak lactate value was recorded before the beginning of CPB ($t_0$), every 60 min during CPB ($t_1$–$t_6$), at the end of surgery ($t_6$), and at the arrival in the intensive care unit (ICU) ($t_0$).

The study primary end-point was the number of children achieving normalization of lactate value, i.e., blood lactate ≤2 mM/l during CPB at a fenoldopam dose of 0.2 µg/kg/min.

The calculation of sample size was based on historical data of a cohort of patients who underwent cardiac surgery at our institute from January 2007 until December 2008 presenting demographic and clinical characteristics similar to those proposed in the present study and meeting the inclusion and exclusion criteria of this study (Table 1). In these historical controls, the incidence of hyperlactataemia was about 40%.

Therefore, a decrease in hyperlactataemia from 40 to 20% was expected in patients receiving fenoldopam treatment during CPB. Applying the Simon’s two-stage optimal design for dose/effectiveness [15] to distinguish a response rate of $p_1 = 0.80%$ from that of $p_0 = 0.60%$, with 90% statistical power and 5% type I error rate, the required total sample size was 53 subjects.

The first stage of the study required the enrolment of 19 evaluable patients. In case of 12 or fewer patients showing blood lactate ≤2 mM/l during CPB, the study had to be terminated at stage 1, and the treatment was considered inadequate and abandoned (rejection). If there were 13 or more patients with normal lactate values, the study had to continue to stage II by enrolling an additional 34 patients up to a total of 53 children. The null hypothesis had to be rejected if there were 37 or more responses among the 53 evaluable patients.

The results are expressed as mean and standard deviation (SD) for continuous variables and absolute and relative frequencies for categorical variables. Parameters of the two groups were compared using Student’s t-test for continuous variables and χ² or Fisher’s exact test for categorical variables. A P-value of <0.05 was considered statistically significant and all P-values were based on two-tailed tests. Statistical analysis was performed using SPSS for Windows (SPSS, Inc., Chicago, IL, USA).

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### Table 1: Demographic characteristics of enrolled patients (fenoldopam group) and historical group, and main cardiopulmonary bypass (CPB) features

<table>
<thead>
<tr>
<th>Characteristics of patients</th>
<th>Fenoldopam group</th>
<th>Historical group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total, n</td>
<td>53</td>
<td>50</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>29 (54%)</td>
<td>27 (54%)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>24 (45%)</td>
<td>23 (45%)</td>
</tr>
<tr>
<td>Aristotle score</td>
<td>8.5</td>
<td>8.1</td>
</tr>
<tr>
<td>Median (range)</td>
<td>8 (3.5; 11)</td>
<td>7.9 (3.5; 11)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± standard deviation</td>
<td>6.5 ± 2.7</td>
<td>7 ± 2.9</td>
</tr>
<tr>
<td>Median (range)</td>
<td>6 (3; 14.8)</td>
<td>6.7 (3; 15.6)</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± standard deviation</td>
<td>0.33 ± 0.09</td>
<td>0.38 ± 0.07</td>
</tr>
<tr>
<td>Median (range)</td>
<td>0.32 (0.2; 0.65)</td>
<td>0.41 (0.24; 0.71)</td>
</tr>
<tr>
<td>CPB (min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>97.2 ± 34.6</td>
<td>99.5 ± 31.6</td>
</tr>
<tr>
<td>Median (range)</td>
<td>89 (60; 173)</td>
<td>92 (60; 181)</td>
</tr>
<tr>
<td>Aortic cross-clamp (min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± standard deviation</td>
<td>63.6 ± 23.7</td>
<td>61.6 ± 26.3</td>
</tr>
<tr>
<td>Median (range)</td>
<td>57 (25; 120)</td>
<td>56 (30; 130)</td>
</tr>
<tr>
<td>Intraoperative diuresis (ml kg⁻¹)</td>
<td>5.04 ± 4.9</td>
<td>4.46 ± 3.9</td>
</tr>
<tr>
<td>Median (range)</td>
<td>3.9 (1.8; 3.6)</td>
<td>3.4 (1.2; 3.0)</td>
</tr>
<tr>
<td>Intraoperative fluid balance (ml)</td>
<td>+20</td>
<td>+25</td>
</tr>
<tr>
<td>Intraoperative blood balance (ml)</td>
<td>+70</td>
<td>+79</td>
</tr>
</tbody>
</table>
RESULTS

Fifty-seven patients were enrolled between March 2009 and February 2012 and 4 of them were excluded because they did not meet the inclusion criteria (1 for CPB time >180 min, 1 for CPB on hypothermia and circulatory arrest, and 2 for CPB time <60 min).

In the first stage, 19 patients were enrolled and 18 (95%) had blood lactate level ≤2 mM/l. Then the study was continued to stage II by enrolling an additional 34 patients.

All the demographic and clinical characteristics of our population are reported in Table 1.

Enrolled patients were 29 males (54.7%) and 24 females (45.3%); the median age at surgery was 5.7 months (range 11 days to 48 months); the median weight and the BSA were 6 kg and 0.32 m², respectively, with a wide range of variation in the sample (3–14.8 kg in weight and 0.2–0.65 m² in BSA).

Surgery details are given in Tables 2 and 3. CPB had a median duration of 89 min (range 60–173 min) and the aortic clamping time was 57 min (range 25–120 min). Perfusion pressure was maintained at a mean value of 53 ± 11.3 mmHg with an average pump flow of 110 ml/kg during CPB. For all patients, adequacy of perfusion was confirmed by ScvO₂ values maintained on average at 75.1 ± 7.2% at time t₁ and 71.4 ± 6.7% at the end of CPB (time t₄). In all patients, we monitored NIRS values, showing good and stable brain perfusion.

During CPB, the patients had a mean diuresis of 5.04 ± 4.9 ml/kg (median 3.9 ml/kg, range 1.8–36 ml/kg) with an average water and blood balance at the end of CPB of +20 and +70 ml, respectively.

At the end of surgery, glycaemic values were <150 mg/dl in 40 patients (75.5%).

During CPB, the primary end-point was achieved in 96.2% of children who had a blood lactate level ≤2.0 mM/l.

The lactate value for CPB time >120 min (range 120–173 min) was 1.79 ± 1.6 mM/l in 14 patients, while it was 1.13 ± 0.4 mM/l in the remaining 39 patients (P = 0.02).

We observed a trend towards an increase in blood lactate levels from the end of CPB until admission to the ICU (Table 3) (Fig. 1). The lactate values during CPB are plotted in Fig. 2.

Fenoldopam infusion was well tolerated in all patients, it did not cause any side effect and none of our patients required discontinuation of infusion for the onset of drug-related tachycardia or hypotension.

DISCUSSION

Hyperlactataemia during CPB is frequently observed even in the absence of signs of overall hypoperfusion and has been interpreted as an early sign of regional hypoperfusion and altered microcirculation [3]. This study showed that intraoperative fenoldopam infusion at a dose of 0.2 µg/kg/min was associated with a low percentage of paediatric cardiac surgical patients with blood lactate >2 mM/l. These findings are clinically relevant because intraoperative elevation of blood lactate was...
Fenoldopam mesylate is a selective DA1 receptor agonist extensively studied in adults for its ability to increase renal blood flow, urinary sodium excretion and urinary output, as well as for its anti-hypertensive effects [10, 11, 16, 17]. A meta-analysis of randomized, placebo-controlled clinical trials in adults undergoing cardiac surgery showed that fenoldopam infusion at the dose range of 0.1–0.3 µg/kg/min reduced acute kidney injury [18].

Fenoldopam has not been approved by the US Food and Drug Administration and European Medicines Agency for use in children so far, and there are still limited published data describing its use in the paediatric population [13, 19–21]. Hammer et al. [13] proved that fenoldopam is a rapid-acting, effective agent for the intravenous control of blood pressure at a dose range of 0.8–1.2 µg/kg/min. A retrospective review [21] of critically ill paediatric patients showed a beneficial effect of fenoldopam on urine output without any detrimental haemodynamic effects. Two reports in paediatric cardiac surgery described the effects of fenoldopam infusion at the dose range of 0.1–0.3 µg/kg/min during the postoperative period, although the results concerning the beneficial effect on urine output were discordant [19, 20]. Only one biomarker study described the intraoperative use of this drug in paediatric cardiac surgery; the authors concluded that high-dose fenoldopam significantly decreased the urinary levels of specific biomarkers of ischaemic injury [21].

To date, no studies have been reported on the effect of fenoldopam infusion on lactate production during CPB in paediatric patients. An increase in lactate levels in a critical setting means an impairment of regulatory mechanisms of lactate production and liver catabolism [1, 3]. Splanchnic perfusion during CPB is difficult to monitor and the only available studies are on adults. In a study on patients undergoing coronary artery surgery, the authors demonstrated that, during hypothermic CPB, hepatic blood flow was reduced and suggested that fenoldopam may have a hepatoprotective effect [22]. Another report on adult cardiac surgical patients suggested that fenoldopam can improve splanchnic blood flow and mucosal microcirculation [23]. Regarding paediatric patients, it is well known that low-weight children are more susceptible than adults to changes in regional vasomotor tone and microcirculation impairment that can occur during CPB [1, 22].

Although the randomized controlled trial is the gold standard to evaluate efficacy and safety of a medicinal product, the vulnerable population eligible for the current study led us to use Simon’s two-stage optimal design for a dose/effectiveness clinical study [24].

On the basis of our retrospective study on our historical population demonstrating the appearance of hyperlactataemia during CPB in about 40% of cases, the present study was aimed at investigating whether fenoldopam mesylate infusion could maintain blood lactate levels ≤2 mM during CPB in paediatric cardiac surgery.

In the attempt to exclude all possible confounding factors, we used the same CPB management both in the historical population and in the fenoldopam group; namely the pump prime was the same, pump flows were determined in both groups according to the patients’ body surface area and, in all cases, electrolyte and acid-base homoeostasis was maintained by means of frequent intraoperative blood gas analyses.

In our children, fenoldopam infusion led to normalization of lactate levels in 96.2% of cases, and it was well tolerated without any adverse event. In the subgroup of patients with CPB time >120 min and with assumed risk of hyperlactataemia because of complex surgical procedures, the blood lactate peak did not exceed 2.0 mM/l. This finding supports our hypothesis that fenoldopam infusion is effective in preventing intraoperative hyperlactataemia during paediatric cardiac surgery.

We observed a trend towards an increase in the blood lactate level from the end of CPB until admission to the ICU, and this was interpreted as a consequence of rewarming and an increased metabolic rate.

In agreement with Ricci et al. [20], during CPB we observed both a reduction in mean blood pressure, which still remained above our protocol-specified limit (i.e. >45 mmHg), and high blood flow related to vasodilatation (average 110 ml/kg).

A randomized placebo study on adults undergoing complex cardiac surgery [23] showed that fenoldopam increased DO2 during CPB, but did not reduce blood lactate production. However, fenoldopam infusion was effective for the reduction of
the blood lactate peak in a subgroup of patients receiving catecholamines for a low cardiac output state. This finding supports the hypothesis that fenoldopam exerts a protective action against vasoconstriction of the splanchnic area induced by endogenous and exogenous catecholamines. As reported in the literature [25], the sympathomimetic hormone response to surgical stress is extreme in neonates compared with adults. Also the detrimental effects of haemodilution, hypothermia and non-pulsatile flow on microcirculation are much more important in small patients compared with adults.

A limitation of our study may be that it was uncontrolled in nature and could not exclude selection bias compared with historical controls, even if we tried to exclude all possible confounding factors. In particular, we used the same CPB management both in the historical population and in the fenoldopam group.

**CONCLUSION**

This is the first clinical study investigating the dose/effectiveness of fenoldopam infusion at 0.2 µg/kg/min in reducing the occurrence of hyperlactaemia during CPB in paediatric patients undergoing cardiac surgery.

We observed that the infusion of fenoldopam during CPB in low-weight patients was well tolerated even in case of complex cardiopathies and, in 96.2% of patients, a blood lactate level <2.0 mM/l was obtained.

Further studies investigating the effect of fenoldopam mesylate in different critical settings in the paediatric population are necessary.

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**REFERENCES**


