Inhaled iloprost to control residual pulmonary hypertension following pulmonary endarterectomy

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Abstract

Objective: Pulmonary endarterectomy (PEA) is the standard therapy for patients with chronic thromboembolic pulmonary hypertension (CTEPH). In the immediate postoperative period, persistent pulmonary hypertension increases the risk of acute respiratory or right heart failure. In pulmonary arterial hypertension, prostanoid inhalation has been found to improve pulmonary hemodynamics, right ventricular function, gas exchange, and clinical outcome. We report the results of a double-blinded randomized trial with the aerosolized prostacyclin analogue iloprost in patients with residual pulmonary hypertension after PEA. Methods: Twenty-two patients (age, 55 ± 13 years; 8 females; propofol- and sufentanil-based anesthesia; pressure-controlled mechanical ventilation) were randomized to receive either a single dose of 25 μg aerosolized iloprost (iloprost group; n = 11) or normal saline (placebo group; n = 11) immediately after postoperative ICU admission. Primary endpoints were changes in gas exchange, pulmonary and systemic hemodynamics, and clinical outcome. Results: Iloprost significantly enhanced cardiac index (CI) and reduced mean pulmonary arterial pressure (mPAP) and pulmonary vascular resistance [PVR (dyn s cm⁻²)] in contrast to placebo. Placebo: pre-inhalation 413 ± 195 versus post-inhalation 404 ± 196 at 30 min (p = 0.051), 415 ± 189 at 90 min (p = 0.929). Iloprost: pre-inhalation 503 ± 238 versus post-inhalation 328 ± 215 at 30 min (p = 0.001), 353 ± 156 at 90 min (p = 0.003). Blood oxygenation remained unchanged. Conclusion: In addition to the effect of PEA, iloprost reduces residual postoperative pulmonary hypertension, decreases right ventricular afterload and may facilitate the early postoperative management after PEA.

Keywords: Hypertension; Pulmonary; Prostanoid; Pulmonary endarterectomy

1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is defined as a distinct form of pulmonary arterial hypertension in the WHO classification of pulmonary hypertension [1]. With a median survival rate of 2.8 years, spontaneous prognosis is as poor as in primary pulmonary hypertension [2]. However, with pulmonary endarterectomy (PEA), a curative surgical treatment option exists for symptomatic patients with CTEPH. Significant improvement and even normalization of hemodynamics and clinical symptoms can be achieved and maintained on a long-term basis [3]. A striking improvement in long-term outcome of operative survivors, however, is still associated with a relatively high perioperative morbidity and mortality rates of up to 10% which occurs almost exclusively during the first few days after surgery. Special factors associated with mortality after this procedure are reperfusion lung injury and right ventricular failure related to residual pulmonary hypertension [2]. Whereas persistent postoperative pulmonary hypertension is usually due to unsuccessful surgery, a residual degree of pulmonary hypertension may result from both the operative trauma and the pulmonary dysfunction associated with cardiopulmonary bypass (CPB), even after successful mechanical endarterectomy of the pulmonary vasculature [4]. Cardiopulmonary bypass-related lung injury can aggravate the pulmonary reperfusion injury and may manifest itself clinically as reperfusion pulmonary edema after PEA. Supportive therapy, as with other forms of acute lung injury, is usually combined with vasodilator and inotropic medication [5]. The administration of selective pulmonary vasodilators was the subject of several case reports and clinical studies aiming at improving postoperative pulmonary hemodynamics, gas exchange, and mortality [6]. None of the human studies demonstrated compelling evidence of benefits regarding mortality or major morbidity. A recent randomized controlled trial of inhaled nitric oxide (NO) after PEA did not show a reduction in the incidence of pulmonary reperfusion edema, in the duration of mechanical ventilation, or in perioperative mortality [7]. In contrast, in primary pulmonary hypertension and in patients...
with CTEPH not eligible for surgery, inhalative treatment with the stable prostacyclin analogue iloprost improved symptoms, hemodynamics, and prognosis [8]. A prospective observational study at our institution demonstrated short-term hemodynamic benefits of postoperative high-dose iloprost inhalation after PEA without major systemic side effects, whereas preoperative administration did not show any beneficial result and even led to systemic hypotension [9]. We therefore aimed to confirm the efficacy of postoperative iloprost inhalation in the short-term improvement of pulmonary hemodynamics and gas exchange in a randomized placebo-controlled study.

2. Methods

Twenty-two patients [14 men and 8 women with a median age of 62 years (ranging from 24 to 76 years)] were prospectively enrolled between March 2001 and April 2002 after obtaining written informed consent to the study according to the Declaration of Helsinki [10]. The study protocol had been approved by the State’s independent Ethics Committee. The patients had been referred to our department with a presumptive diagnosis of CTEPH [NYHA functional class II (n = 4), class III (n = 11), and class IV (n = 7)] and, after completion of the diagnostic work, were considered candidates for PEA. They were randomized into two groups (n = 11 each) following a randomization list edited by the institutional Clinical Study Coordination Center, whose members were unaware of patients’ identities. Emergency or redo procedures were excluded. Biometric and preoperative data of the two groups (placebo vs iloprost) are summarized in Table 1.

For patients randomized into the placebo group, 2.0 mL of 0.9% saline solution was used. For the verum group, a dose of 25 μg iloprost (Ilomedin®, Schering GmbH, Berlin, Germany) was diluted with saline to a total volume of 2.0 mL. The time point of inhalation was after admission to postoperative iloprost inhalation in the short-term improvement of pulmonary hemodynamics and gas exchange in a randomized placebo-controlled study.

### Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Iloprost group (n = 11)</th>
<th>Placebo group (n = 11)</th>
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</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>54 ± 17</td>
<td>56 ± 13</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.98 ± 0.2</td>
<td>1.88 ± 0.2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77 ± 10</td>
<td>73 ± 13</td>
</tr>
<tr>
<td>Female sex (number)</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>NYHA functional class (II/III/IV)</td>
<td>2/6/3</td>
<td>2/5/4</td>
</tr>
<tr>
<td>Cardiac index (L min⁻¹ m⁻²)</td>
<td>2.0 ± 0.7</td>
<td>2.2 ± 0.5</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure (mmHg)</td>
<td>45 ± 13</td>
<td>47 ± 15</td>
</tr>
<tr>
<td>Pulmonary-artery wedge pressure (mmHg)</td>
<td>8 ± 2</td>
<td>10 ± 2</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (dyn s cm⁻³)</td>
<td>768 ± 234</td>
<td>789 ± 312</td>
</tr>
<tr>
<td>Central venous pressure (mmHg)</td>
<td>11 ± 2</td>
<td>12 ± 3</td>
</tr>
<tr>
<td>Mean blood pressure (mmHg)</td>
<td>85 ± 8</td>
<td>82 ± 9</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyn s cm⁻³)</td>
<td>1105 ± 340</td>
<td>1138 ± 287</td>
</tr>
<tr>
<td>PaO₂ (mmHg)</td>
<td>63 ± 11</td>
<td>63 ± 14</td>
</tr>
<tr>
<td>PaCO₂ (mmHg)</td>
<td>32 ± 3</td>
<td>33 ± 4</td>
</tr>
<tr>
<td>Mixed venous oxygen saturation (%)</td>
<td>60 ± 8</td>
<td>61 ± 8</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>83 ± 12</td>
<td>81 ± 15</td>
</tr>
</tbody>
</table>

*Plus-minus values are mean ± standard deviation. NYHA denotes New York Heart Association; PaO₂, partial pressure of arterial oxygen; PaCO₂, partial pressure of arterial carbon dioxide (measured while the patient was breathing ambient air). There were no significant differences between the iloprost and the placebo groups.
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Table 2
Baseline hemodynamics, arterial and venous oxygenation after postoperative ICU admittance and status at hospital discharge

<table>
<thead>
<tr>
<th>Variable</th>
<th>ICU admittance</th>
<th>Hospital discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Iloprost group</td>
<td>Placebo group</td>
</tr>
<tr>
<td>Cardiac index (L min⁻¹ m⁻²)</td>
<td>2.8 ± 0.7</td>
<td>2.6 ± 0.5</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure (mmHg)</td>
<td>36 ± 11</td>
<td>38 ± 13</td>
</tr>
<tr>
<td>Left atrial pressure (mmHg)</td>
<td>8 ± 2</td>
<td>10 ± 2</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (dyn s cm⁻²)</td>
<td>503 ± 238</td>
<td>413 ± 196</td>
</tr>
<tr>
<td>Right atrial pressure (mmHg)</td>
<td>11 ± 5</td>
<td>10 ± 4</td>
</tr>
<tr>
<td>Mean blood pressure (mmHg)</td>
<td>85 ± 8</td>
<td>82 ± 9</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyn s cm⁻²)</td>
<td>1059 ± 327</td>
<td>1117 ± 239</td>
</tr>
<tr>
<td>Ratio of arterial oxygen tension/fraction of inspired oxygen (mmHg)</td>
<td>262 ± 73</td>
<td>300 ± 78</td>
</tr>
<tr>
<td>Mixed venous oxygen saturation (%)</td>
<td>68 ± 6</td>
<td>67 ± 7</td>
</tr>
</tbody>
</table>

a Values are mean ± standard deviation.
b Fraction of inspired oxygen was set as 0.21 while the patient was breathing spontaneously.
c p values for the comparison of iloprost with the placebo group.
d p < 0.05 in comparison to values at ICU admittance.

Results

3.1. Process and outcome variables

Mean duration of cardiopulmonary bypass did not differ between groups (Iloprost: 303 ± 44 min vs placebo: 305 ± 75 min; p = 0.951). Also, duration of deep hypothermic circulatory arrest was comparable (Iloprost: 43 ± 13 min vs placebo: 37 ± 11 min; p = 0.248).

Perioperative mortality was 0/11 patients in the iloprost group and 1/11 patients in the placebo group (p = 0.957). The single death in the placebo group occurred 4 days postoperatively and was due to persistent pulmonary hypertension with acute right heart and subsequent multi-organ failure.

In the survivors, mean duration of mechanical ventilation did not differ between groups (Iloprost: 31 h, range 8—120 h vs placebo: 38 h, range 6—96 h; p = 0.504). All survivors of both the groups experienced significant improvements in hemodynamic parameters and clinical symptoms at hospital discharge, when compared with their preoperative status (Tables 1 and 2).

3.2. Hemodynamic data

Pulmonary endarterectomy per se was associated with a significant improvement of pulmonary hemodynamics in all patients on admission to ICU. Postoperative baseline data recorded prior to inhalative treatment did not differ significantly between the groups (Table 2). In the placebo group, neither systemic and pulmonary hemodynamics nor gas exchange changed significantly during and after completion of aerosol inhalation. Also, no changes were observed 30, 60, and 120 min after the start of the inhalation period (Figs. 1 and 2).

In all patients of the iloprost group, mean PAP started to decrease within the first few minutes of inhalation beyond the degree of PAP reduction already produced by PEA. The maximum reduction occurred between 20 and 30 min after the start of iloprost inhalation, the minimum mean PAP being 27.0 ± 4.4 mmHg (difference from baseline: −11.0 ± 1.1 mmHg; p = 0.005 vs placebo: −2.2 ± 1.7 mmHg; p = 0.718). A return to baseline values occurred after 90—120 min (Fig. 1A). Simultaneously, cardiac index increased from 2.8 ± 0.7 L min⁻¹ m⁻² to a maximum of 3.4 ± 0.7 L min⁻¹ m⁻² (difference from baseline: +0.6 ± 0.1 L min⁻¹ m⁻²; p = 0.002 vs placebo: −0.04 ± 0.1 L min⁻¹ m⁻²; p = 0.313; Fig. 1B). Iloprost inhalation decreased PVR significantly to a minimum of 320 ± 196 dyn s cm⁻¹² (difference from baseline: −183 ± 88 dyn s cm⁻¹²; p = 0.001 vs placebo: −16 ± 38 dyn s cm⁻¹²; p = 0.577; Fig. 1C). Systemic hemodynamics, and specifically, SVR, remained unaffected at any time point of measurement (Fig. 1D). At hospital discharge, pulmonary hemodynamics and cardiac output had significantly improved from immediate postoperative baseline values without significant differences between the groups (Table 2).

3.3. Gas exchange

Both the groups did not experience any significant changes in their oxygenation index (PaO₂/FIO₂ ratio) both during and after inhalation (Fig. 2). Mixed venous oxygenation, however, tended to increase after iloprost inhalation, showing a small but significant difference to placebo 60 min after the start of inhalation (73.4 ± 3.1% difference from baseline; +3.4 ± 0.7%; p = 0.005; Fig. 2B). One patient in the placebo group with persistent pulmonary hypertension developed severe reperfusion pulmonary edema, acute respiratory distress syndrome, and subsequent multi-organ failure. This patient died on postoperative day 4. At hospital discharge, patients of both the groups had significantly improved arterial oxygenation compared to their early postoperative baseline (Table 2).

3.4. Safety

There were no serious adverse events related to the inhalation of iloprost. A transient facial flush occurred in 4 of 11 patients with iloprost, and in none of the placebo group. There was no significant tachycardia, hypotension or oxygen desaturation observed during inhalation in both the groups. Thus, no antiarrhythmic therapy was necessary, and there was also no difference in the catecholamine management between the groups. Iloprost inhalation did not increase the risk for postoperative bleeding complications. The mean blood loss into the chest drainages was 475 ± 153 mL in the
iloprost group versus 387 ± 174 mL in the placebo group (p = 0.547). Transfusion rate for units of packed red cells in the iloprost group was 7 ± 3 versus 6 ± 4 in the placebo group (p = 0.842). Fatal reperfusion pulmonary edema occurred in one patient in the placebo group, causing the only death and an overall mortality of 5.0%.

4. Discussion

PEA is the treatment of choice for major-vessel CTEPH, since it achieves immediate and sustained reduction of PAP, increases cardiac output and oxygenation and has been shown to improve long-term outcome [2]. PEA is an extensive surgical procedure requiring cardiopulmonary bypass and periods of deep hypothermic circulatory arrest. Ineffective reduction of pulmonary arterial pressure and PVR, frequently accompanied by severe reperfusion pulmonary edema, are reasons for the increased perioperative morbidity and mortality of PEA, when compared to routine cardiac surgical procedures [11]. Unrelenting, persistent pulmonary hypertension after PEA is frequently fatal; it is characteristic of patients with unrecognized or surgically inaccessible distal thromboembolic disease, secondary distal vasculopathy, or primary pulmonary hypertension affecting the pulmonary vasculature beyond the subsegmental level [2]. These conditions render proximal endarterectomy by the surgeon ineffective and should therefore, if suspected during preoperative diagnostic workup, caution against the surgical approach.

However, despite complete endarterectomy in surgically accessible disease with substantial reduction of PVR and concomitant increase of cardiac output, PAP and PVR may still remain elevated temporarily and may sometimes even exceed preoperative levels. This so-called residual postoperative pulmonary hypertension will usually abate within 12—72 h towards the level achieved at hospital discharge. Such a postoperative course does not reflect distal structural disease but transient postoperative pulmonary vasoconstriction.

The etiology of reversible postoperative pulmonary vasoconstriction is thought to be multi-factorial. Mechanical irritation of the pulmonary vessels and ischemia—reperfusion injury from interruption of both pulmonary perfusion and collateral bronchial circulation during hypothermic circulatory arrest are thought to contribute, as well as the activation of pro-inflammatory and vasoconstrictive mediator cascades related to extracorporeal circulation [4]. Clinically, such residual postoperative PVR elevation may precipitate right ventricular failure, endanger pulmonary arterial suture lines, and cause hyperperfusion of endarterectomized pulmonary segments. The latter will aggravate protein leakage into the alveoli, reperfusion pulmonary edema, and hypoxemia.

Mechanisms of post-bypass pulmonary vasoconstriction have been the focus of several research groups. In infant congenital heart disease, Schulze-Neick et al. [12] have studied transient pulmonary endothelial dysfunction (PED) following cardiopulmonary bypass. PED is characterized by a reversibly reduced production of endogenous vasodilators, e.g., NO and prostacyclin, and is associated with post-
operative exacerbation of preoperatively elevated PVR. Vasodilator impairment due to a disturbed L-arginine—NO pathway appeared reversible by the exogenous or the endogenous replacement of nitric oxide. There remains, however, another component of post-bypass pulmonary vasoconstriction, which is not fully restorable via the NO pathway, and has been attributed to increased levels of endothelin-1 (ET-1). ET-1 is a potent vasoconstrictor peptide and smooth-muscle cell mitogen both produced and cleared in the pulmonary circulation. Besides pulmonary vasoregulation mediated by ET-receptor subtypes, ET-1 is thought to induce long-term proliferative vasculopathy. In adults with primary and secondary pulmonary hypertension, increased plasma ET-1 levels have been observed [13]. Also, ET-1-mediated vasoconstriction has been found to occur in patients with secondary pulmonary hypertension after cardiopulmonary bypass [14], and ET-A receptor blockade reduces post-bypass increased PVR [12]. Moreover, iloprost has been shown to ameliorate post-ischemic lung reperfusion injury and to maintain pulmonary ET-1 balance in an isolated lung perfusion model [15].

Current specific pharmacological treatment of post-bypass pulmonary vasoconstriction is aimed at these mechanisms. Inhaled NO has been employed on weaning from CPB in order to induce selective pulmonary vasodilatation and also to improve gas exchange. With such regimens, reductions in time on the ventilator and in the intensive care stay have been shown for children with surgically corrected atrial and/or ventricular septal defects [16]. Following cardiac transplantation, Rajek et al. [17] described a reduced incidence of failure to wean from CPB. A reduced risk of right heart failure has been reported in patients after left ventricular assist device implantation [18]. Following PEA, however, until recently only case reports existed, which indicated that inhaled NO may lower PVR and improve oxygenation [6]. Meanwhile, results of a prospective placebo-controlled randomized trial in 60 postoperative CTEPH patients have been reported, in which 4 h of post-reperfusion inhalative treatment with NO did not significantly reduce the incidence of reperfusion pulmonary edema and — although not powered for this end-point — also did not significantly improve survival [7].

Inhalation of aerosolized iloprost has undergone several clinical trials which showed that it significantly improves cardiopulmonary functional status in medically managed patients with pulmonary hypertension, including those with CTEPH inaccessible to surgery [8]. In the postoperative setting after coronary bypass or valve surgery, two case series reported a reduction of elevated PVR after iloprost inhalation without relevant systemic side effects [19,20]. At our institution, a prospective observational series of 10 CTEPH patients undergoing PEA were inhaled perioperatively with aerosolized saline (control) followed by iloprost; the drug produced no hemodynamic benefits during anesthesia and controlled ventilation prior to surgery but induced clear improvements of pulmonary hemodynamics with only moderate systemic side effects after PEA [9]. Potential toxicity has not been evaluated so far [21]. Compared with inhaled NO, aerosolized iloprost has been described as a more potent pulmonary vasodilator with superior improvement of gas exchange in hypoxemic PPH patients [22]. More recently, iloprost inhalation has been shown to significantly increase the pulmonary clearance, and hence, abolish the pulmonary net release of ET-1 in spontaneously breathing patients with primary, secondary, or thromboembolic ($n = 4$) pulmonary hypertension [23]. Also, in an isolated lung perfusion model in rabbits, iloprost ameliorated post-ischemic lung reperfusion injury and maintained an appropriate pulmonary ET-1 balance [15]. These data support the rationale of our study to test iloprost inhalation in a prospective randomized fashion during early postoperative management after PEA.

The study demonstrated that beyond the effects of PEA upon PVR, a further significant pulmonary vasodilatation could be induced by inhalation of iloprost aerosol in all patients, which was accompanied by an increase in cardiac output. Since, in the pilot study, unintended systemic vasodilatation had occurred during preoperative inhalation of 33 μg iloprost, a reduced dose of 25 μg iloprost per inhalation was used in this series. Indeed, systemic hemodynamics remained unaffected, and largely selective pulmonary vasodilatation was achieved. All patients routinely received norepinephrine (0.1—0.2 μg kg$^{-1}$ min$^{-1}$) via a left atrial catheter to maintain adequate coronary perfusion pressure for the right ventricle; this might have balanced systemic vasodilatation from iloprost to some degree. However, no dose adjustments of systemic vasopressors

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Fig. 2. Changes and time courses of gas exchange parameters in the iloprost (black) and placebo groups (white). (A) Ratio of inspired oxygen tension per fraction of inspired oxygen (PaO$_2$/FiO$_2$); (B) mixed venous oxygen saturation (SvO$_2$). $p < 0.05$ for iloprost versus placebo.
were performed or were necessary during iloprost inhalation. Vasopressor support could be reduced in all patients at the end of the observation period as a consequence of the hemodynamic improvement after iloprost administration. Vasopressor dose or duration of administration in the iloprost group did not differ from that in placebo patients.

In contrast to the results of the randomized iloprost trial in PPH [8], gas exchange did not improve in this study during iloprost inhalation or for 120 min thereafter. Patients in the series of Olschewski et al. received iloprost while breathing ambient air or their long-term oxygen supplement during measurements. Thus, some degree of ventilation/perfusion mismatch may still have been present prior to inhalation. In the present study patients had pressure-controlled mandatory ventilation with arterial blood gases kept in a predefined physiological range to minimize the influence of hypoxemia on PVR. At hospital discharge, both the groups demonstrated improved arterial oxygenation, but patients in the iloprost group had a significantly improved PaO2/FIO2 ratio compared with baseline. Although the survivors showed no difference in their clinical or radiological degree of reperfusion edema, this might have indicated reduced pulmonary injury.

However, in view of the very limited size of the cohort, it must be stressed that this study was neither intended nor powered to assess end-points like incidence of reperfusion pulmonary edema, time on the ventilator or perioperative mortality. Nevertheless, clinical outcomes were definitely not inferior to those of placebo, attesting to the relative safety of the iloprost treatment. In fact, one patient receiving placebo developed severe acute reperfusion pulmonary edema and died from right ventricular failure. Preoperatively, this patient had had severe pulmonary hypertension (mean PAP, 59 mmHg; PVR, 1426 dyn s cm⁻⁵), which increased his risk of perioperative mortality [11]. Such patients might benefit acutely from postoperative iloprost inhalation, and probably, given their unfavorable short- and long-term prospects with this postoperative hemodynamic profile, are considered candidates for combined long-term treatment, e.g., with oral sildenafil and inhalational pulmonary vasodilators [24]. For severe CTEPH, preoperative pretreatment with IV prostacyclin or inhalational iloprost has been studied [25]. Apparently, optimum effects are achieved rather than an extended pretreatment period prior to surgery than by short-term preoperative administration. While Nagaya et al. found improved pulmonary hemodynamics and postoperative survival with a 7-week perioperative course of intravenous prostacyclin, an immediate preoperative trial of inhaled iloprost in our pilot series did not produce selective pulmonary vasodilatation but depressed systemic hemodynamics and cardiac output [9]. So far, sustained clinical benefits for these interventions are proven only in patients with primary pulmonary hypertension [8].

In summary, inhalation of aerosolized iloprost during the early postoperative period after PEA effectively reduced residual post-bypass pulmonary vasoconstriction and improved cardiac output, with a maximum effect after approximately 30 min after the start of drug administration. Gas exchange remained stable, and there were no adverse events attributable to treatment with iloprost in this dose and setup. At this stage, the results suggest that the administration of aerosolized iloprost during the period of residual pulmonary vasoconstriction following PEA is a helpful and safe adjunct to improve pulmonary hemodynamics and cardiac output and thus to facilitate the management of this critical stage of the procedure. In view of these and others' findings, inhaled iloprost should undergo further evaluation in larger series to assess whether it also improves clinical outcome of surgical patients with life-threatening perioperative pulmonary hypertension and compromised right heart function.

4.1. Limitations

Except of the inhalative drug or placebo administration, all patients had to be treated according to an established management protocol after PEA due to ethical reasons. Thus, it was not possible to evaluate other potential doses and dose-effects of iloprost or to discuss cumulative inhalations and their potential effects under double-blinded conditions.

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References


