Role of prostacyclin (epoprostenol) as anticoagulant in continuous renal replacement therapies: efficacy, security and cost analysis

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ABSTRACT: Background: Heparin remains the drug most commonly used for anticoagulation in continuous renal replacement therapies (CRRTs). However, in patients with hypercoagulability, heparin is insufficient or, in cases with an increased risk of bleeding or thrombocytopenia, it may be contraindicated. Epoprostenol, a potent vasodilator, antithrombotic and antiplatelet agent, could be an alternative.

Patients and methods: We studied the records of patients treated under continuous venovenous hemodiafiltration in an academic tertiary hospital of 900 beds, between January 2000 and June 2003. Epoprostenol was prescribed to patients with (i) filter hypercoagulability, defined as consumption of 2 or more filters in the last 24 hours; (ii) low platelet count; or (iii) recent severe hemorrhage.

Results: Thirty-eight out of 248 (15%) patients who were under CRRT received epoprostenol for more than 72 hours. Epoprostenol was indicated due to filter hypercoagulability in 48%, thrombocytopenia in 68% (7 patients both) and hemorrhage in 3% of cases. The overall time for epoprostenol therapy was 9,749 hours. The mean filter duration previous to epoprostenol was 23 ± 12 hours and after administering this drug 38.2 ± 11.9 hours (p=0.0001). In 6 patients, heparin and epoprostenol were simultaneously administered. The adverse effects were hemorrhage, which presented in 7 patients (18%) and a fall in blood pressure in another 7 (18%), which recovered in the next 24 hour after starting treatment. Cost analysis demonstrates some advantage with epoprostenol in patients with increased tendency to clotting.

Conclusions: Epoprostenol may be safely used to prevent clotting of the extracorporeal circuits, either alone in patients with thrombocytopenia and/or increased risk of bleeding, or in combination with heparin in states of hypercoagulability.

Key words: Prostacyclin, Epoprostenol, Prostaglandins, Anticoagulation, Heparin, Continuous renal replacement therapies, Hemofiltration, Hemodiafiltration, Filter duration, Platelets

INTRODUCTION

In critical care patients, continuous renal replacement therapies (CRRTs) are frequently administered in acute renal failure and multiple organ dysfunction settings. Their excellent tolerability is their main advantage in comparison to intermittent hemodialysis, and this relies on gradual fluid and solute removal without sudden osmotic changes. However, the main drawback of this and other extracorporeal techniques, such as the molecular adsorbent recirculating system (MARS) is the necessity for a prolonged anticoagulation of the extracorporeal circuit.

Filter and circuit coagulation represents between 40% and 70% of kit changes, the remainder being due to both programmed and logistic causes, such as surgical interventions or diagnostic procedures (1, 2). Furthermore, system coagulation represents loss of blood (between 100 and 200 mL), nursing time and consumption of fungibles. On the other hand, anticoagulants can pro-
duce systemic effects and bleeding. Thus, there is a struggle between filter coagulation and hemorrhage. Unfractionated sodium heparin (standard heparin) remains the most frequently used agent and the drug of choice for patients who require anticoagulation. It is cheap, and at low dosages (5-10 IU/kg per hour) the systemic effects are minor. However, in some patients who present with hypercoagulability, heparin is insufficient, and in other groups, this drug is contraindicated or at least dangerous, because of a higher bleeding risk or a low platelet count. In addition, continued exposure to heparin may lead to the development of heparin-immunoglobulin G4 complexes and heparin-induced thrombocytopenia type II (THI II), therefore increasing the risk of a combination of bleeding and thrombotic complications (3).

There are several alternatives to heparin in THI II, such as human recombinant hirudin, danaparoid or argatroban (4). However, the drugs most often used in CRRT, apart from heparin, are citrate and prostaglandins. Prostacyclin (PGI₂) is a member of the eicosanoid family of lipid mediators and the major product of the arachidonic acid metabolism, formed in the endothelium. It is a potent vasodilator, antithrombotic and antiplatelet agent that mediates its effects through a membrane-associated receptor: the IP (5). When administered as a drug it is called epoprostenol. Prostacyclin is a potent inhibitor of platelet function (6). PGI₂ reversibly inhibits their function by diminishing the expression of platelet fibrinogen receptors and P-selectin, and it reduces heterotypic platelet-PMN aggregation during continuous venovenous hemofiltration in critically ill patients (7). Prostacyclin has been successfully used in conventional hemodialysis and in CRRT without significant systemic hypotension (8, 9).

With the aim of reporting our experience with epoprostenol as anticoagulant in CRRT we reviewed our casistics, evaluating the causes which prompted us to use it, analyzing costs and security profiles.

**Patients and methods**

**Setting**

We studied the records of patients treated with CRRT in an academic tertiary hospital of 900 beds, between January 2000 and June 2003.

**Design**

This was a retrospective analysis, with each patient in control of himself or herself before and after epoprostenol prescription.

**Technique**

The CRRT prescribed was continuous venovenous hemodiafiltration (CVVHDF) using in all cases filters of AN69-polyacrylonitrile membrane ranging from 0.6 to 1 m², and monitoring by means of either a Prisma (Hospal-Cobe Renal) or, less frequently (see below for details), a BSM22 (Hospal) machine. The extracorporeal blood flow (QB) was programmed from 100 to 150 mL per minute, the dialysate flow (Qd) 1,000 mL per hour and the reinfusion (Qr) ranged from 500 to 2,000 mL per hour with specific hemofiltration fluids (E2, Bi-effe Medital; and B0, Hospal) or Ringer lactate. The reinfusion was administered in the predilution stage (pre-filter) in order to reduce the filtration fraction in all patients, except in 6 cases.

**Anticoagulation**

In normal conditions, unfractionated heparin was administered at the entrance of the circuit (pre-filter) at a dosage of 5 to 10 IU/kg body weight (mode 500 IU) per hour. Doses were then regulated – depending on laboratory parameters, such as activated partial thromboplastin time (APTT) – to obtain values between 35 and 45 seconds, and on clinical data such as bleeding and filter duration. Indications of no anticoagulation are referred in Table I, in agreement with those reported by Bellomo et al (10).

**Filter hypercoagulability**

Filter hypercoagulability was defined by increased tendency to clotting with consumption of 2 or more filters in the previous day, and after ruling out malfunction of the central venous catheter.

**Epoprostenol administration**

Prostacyclin was prescribed to patients with (i) filter hypercoagulability alone or in association with low-dose heparin; (ii) low platelet count of any etiology; or (iii) recent severe hemorrhage. Epoprostenol was administered at the entrance of the circuit at an initial dosage

**Table I** - Criteria for No Anticoagulation: Patient Fulfilled 1 of These

<table>
<thead>
<tr>
<th>Platelet count &lt;50x10⁹/L</th>
<th>APTT &gt;60 s</th>
</tr>
</thead>
<tbody>
<tr>
<td>International normalized ratio (INR) for prothrombin &gt;2</td>
<td></td>
</tr>
<tr>
<td>Presence of disseminated intravascular coagulation (DIC)</td>
<td></td>
</tr>
<tr>
<td>Presence of spontaneous bleeding</td>
<td></td>
</tr>
</tbody>
</table>

*Source (10).*
of 5 ng/kg body weight per minute (5 ng·kg⁻¹·min⁻¹) protected from light and no more than 12 hours at room temperature.

**Vascular access**

Percutaneous polyurethane dual lumen catheters (Arrow: 12 French [12F] in diameter and 16-20 cm in length) were placed into femoral, subclavian or internal jugular veins. Two patients had a tunneled 13F Hickman catheter placed in the internal jugular.

**Patients**

The cohort was separated into 2 groups: group 1 comprised patients who received circuit anticoagulation with epoprostenol as first election for more than 72 hours, and group 2 comprised patients who received epoprostenol for more than 72 hours as a second step (i.e., following heparin or no anticoagulant).

**Statistical analysis**

Data are expressed as mean ± standard deviation. Paired Student’s t-tests and Wilcoxon tests were performed to compare pre- and post-epoprostenol data, based on the sample data distributional features.

**RESULTS**

**Frequency, demographic and etiological data**

During the study period (42 months), 248 patients were treated with CRRT. Of them, 38 (15%) received epoprostenol (29 men and 9 women, mean age 56.5 ± 13.3 years, range 30-77 years). All patients suffered from multiorgan failure (MOF) with at least 2 other organs that had failed apart from the kidney insufficiency. The total time of CRRT patients receiving epoprostenol was 9,749 hours. The mean dosage was 22.4 ± 3.6 µg·h⁻¹ (75th percentile: 24.2 µg·h⁻¹).

**Group 1**

Ten patients were included in this group. Eight of them due to thrombocytopenia, 1 for recent bleeding and the other 1 for hypercoagulability (diagnosed in a previous episode of CRRT).

**Group 2**

Twenty-eight patients were included in this group; 18 of them due to thrombocytopenia and in the other 10 due to hypercoagulability. The cause of intensive care unit (ICU) admission is shown in Table II. The average filter consumption per patient pre- and post-epoprostenol was similar (7.4 ± 4.9 filters vs. 7.1 ± 4.9 filters, respectively; p=0.7).

**Filter life-span**

The mean filter duration in the 38 patients during epoprostenol administration was 38 ± 13 hours (Fig. 1). In group 2, the pre-epoprostenol duration was 23 ± 12 hours and after administering epoprostenol it was 38.2 ± 11.9 hours (p=0.0001), while in patients with filter hypercoagulability, duration was 19.9 ± 10.2 hours and 35.2 ± 9.9 hours, respectively (p=0.0029).

Filters were electively re-changed every 72 hours with Prisma machines and every 48 hours with BSM22. The former was used in 27 out of 38 patients and the latter in 16 (5 patients alternated both monitors). The filter consumption rate previous to epoprostenol administration was 1.5 ± 1.3 filters per day (in the hypercoagulability subgroup, 1.92 per day), and post-epoprostenol administration was 0.7 ± 0.3 filters per day (p=0.0022).

**Epoprostenol plus heparin**

In 6 out of 38 patients, heparin and epoprostenol were simultaneously administered. They were from group 2; they received epoprostenol alone (4 patients due to filter hypercoagulability and the other 2 due to thrombocytopenia), and the cause of the simultaneous prescription was the ineffectiveness of epoprostenol alone. In these patients, the dosages of epoprostenol and the maximum and minimum dosages of heparin are shown in Table III. Three patients received very low dosages of heparin and the remainder needed higher
dosages. In this subgroup the filter duration was 31.6 ± 10.3 hours, whereas their previous mean duration was 14.8 ± 8.9 hours (p=0.07).

Adverse effects

Hemorrhagic complications, defined as evident bleeding in mucosa, wound or natural or artificial orifices were present in 7 out of 38 patients (18%). In 5 of them, blood transfusion was necessary and epoprostenol was subsequently discontinued, resolving this complication in the first hour. In the other 2 patients neither transfusion nor drug suspension was performed. There were no deaths attributed to this complication. The patient who was administered epoprostenol for bleeding after being treated with heparin, recovered from this complication.

Platelet count, in the subgroup of patients with thrombocytopenia, showed a trend toward an increase at the end of treatment, raising from 52,736 ± 31,090 to 88,421 ± 74,978 cells per µL (p=0.061).

Arterial hypotension, defined as a fall of systolic blood pressure below 100 mm Hg, requiring an increment in vasoactive drugs, occurred in 7 out of 38 patients (18%). The mean diastolic decrement in these 7 patients was 12.57 ± 8.9 mm Hg. The pre-epoprostenol systolic blood pressure (SBP) in these 7 patients was 122 ± 16 mm Hg and in the remainder 128 ± 20 mm Hg (n.s.). One hour after starting epoprostenol administration SBP was 115 ± 22 and 94 ± 12 mm Hg, respectively. In all of them the treatment continued and the blood pressure recovered to baseline levels in the following 24 hours (Fig. 2). During the study period, epoprostenol was prescribed to 4 other patients, but none of them fulfilled the 72-hour duration of administration criterion. In 1 of these patients, severe hypotension developed, which forced us to withdraw epoprostenol administration, and a second attempt led to the same results.

Cost analysis

We performed simple calculations assuming a similar price (as is the case in our center) between 1 hemofiltration kit (filter plus lines) and 1 epoprostenol vial (approximately €130). Once the epoprostenol vial is reconstituted, its durability at room temperature is 12 hours and 24 to 36 hours in the fridge. So, depending on the patient’s body weight, from 1 vial (500 µg per vial) we can get either 1 or 2 diluted solutions which

| TABLE II - CAUSES OF ADMISSION TO INTENSIVE CARE UNIT |
|-------------------------------|----------------|----------------|
| Cause                        | Number of patients | Comments (number of patients) |
| Sepsis                                         | 20              | Renal transplant patients (2)                   | Single (1) |
| Nonseptic shock                    | 8               | Hypovolemic (2)                                      | Liver and kidney (1) |
| Cardiac surgery (6)               |                  |                                                  | Renal transplant (2) |
| Hepatic failure                    | 3               | Hepatic and renal failures (3)                             | Paracetamol poisoning (1) |
| Neurological                       | 1               | Subarachnoid hemorrhage (1)                               | Chronic renal failure (1) |
| Trauma                           | 2               | Polytrauma (2)                                             | Rhabdomyolysis (1) |
| Burns                            | 3               |                                                  |                     |
| Acute pancreatitis                | 1               |                                                  |                     |
| Total                            | 38              |                                                  |                     |

| TABLE III - DOSAGES OF EPOPROSTENOL AND HEPARIN IN PATIENTS WHEN RECEIVING BOTH DRUGS |
|-------------------------------|----------------|----------------|
| Patient number | Epoprostenol dosage (µg/hour) | Minimal heparin dosage (U/hour) | Maximal heparin dosage (U/hour) |
| 8               | 30              | 500            | 1,250                        |
| 12              | 30              | 250            | 250                          |
| 14              | 27              | 125            | 375                          |
| 22              | 25              | 125            | 500                          |
| 25              | 20              | 125            | 125                          |
| 34              | 21              | 1,000          | 1,000                        |
Epoprostenol in continuous renal therapies

will last for 1 or 2 periods of 12 hours. Patients weighing less than 69 kg only need 1 vial of epoprostenol per day (5 ng·kg⁻¹·min⁻¹ 69 kg·1,440 min = 496.8 µg). We had previously calculated nursing time for the change of filters (76 ± 16 minutes). The wage per nephrology-nurse hour was €16.46. The results are shown in Table IV. In this analysis we did not take into account the loss of blood of the patients (approximately 200 mL per filter coagulated) and the time lost in their treatment.

**DISCUSSION**

In this study we have found prostacyclin to be an efficient alternative to heparin. Prostacyclin was prescribed to improve the life-span of filters and extracorporeal circuits. In the 28 patients of group 2, the post-prostacyclin duration was 60% higher than that measured previously, and in those patients with filter hypercoagulability it nearly doubled the previous filter life-span. Furthermore, the filter life-span provided by epoprostenol outlasts that reported by us in a previous series of 350 filters in which most of the patients (45 out of 50) had only been treated with heparin (39 vs. 30 hours) (2). The security profile of PGI₂ is good. The follow-up of near 10,000 hours of treatment only demonstrated a few episodes of hypotension and bleeding – obviously not to be attributed entirely to prostacyclin administration.

The cost analysis reveals that using epoprostenol in selected cases (patients with thrombocytopenia or in addition to heparin in states of hypercoagulability) we can improve the efficacy at a reasonable cost (similar cost if the patient’s body weight is less than 69 kg). We realize that cost analysis may be different in other countries.

Hypercoagulability is relatively frequent in ICU patients, mainly in the acute phase of the systemic inflammatory response syndrome and sepsis. This may be due to circulating procoagulant factors and decreased levels of antithrombin III, which hampers the effect of heparin.

Prostacyclin has been used as an alternative to heparin for anticoagulation in CRRT. PGI₂ offers a number of theoretical advantages due to its antiinflammatory and anticoagulant properties. The vasodilator effect of prostaglandins may be beneficial. In patients suffering from septic shock, some investigators have observed that prostacyclin increases oxygen delivery and its extraction by the tissues. The increase in splanchnic blood flow prevents the translocation of bacteria and toxins (11). In healthy humans, infusion of prostacyclin at 2, 4 and 8 ng·kg⁻¹·min⁻¹ increases renal plasma flow, angiotensin II, atrial natriuretic peptide and heart rate, and decreases mean blood pressure (12).

**TABLE IV - SIMPLE COST ANALYSIS OF HEMODIAFILTRATION**

<table>
<thead>
<tr>
<th>Filters/Kit/Cost</th>
<th>Anticoagulant/Time</th>
<th>Cost of nurse to change filters</th>
<th>Total cost per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filters/day</td>
<td>Kit cost (€)</td>
<td>Anticoagulant (€)</td>
<td>Cost of nurse time</td>
</tr>
<tr>
<td>Pre-epoprostenol (n=28)</td>
<td>1.5</td>
<td>125 Heparin (or nothing)</td>
<td>2.40</td>
</tr>
<tr>
<td>Hypercoagulability (n=11)</td>
<td>1.9</td>
<td>125 Heparin</td>
<td>2.40</td>
</tr>
<tr>
<td>Post-epoprostenol (n=38)</td>
<td>Body weight &lt;69 kg</td>
<td>0.7</td>
<td>125 Epoprostenol (1 vial)</td>
</tr>
<tr>
<td>Body weight &gt;69 kg</td>
<td>0.7</td>
<td>125 Epoprostenol (2 vials)</td>
<td>252.00</td>
</tr>
</tbody>
</table>

Nurse time cost is calculated at €16.46/hour. The heparin cost was calculated assuming an average dosage of 500 IU per hour. Reposition or dialysis fluids and other consumptions or charges are not included because there are no differences before and after epoprostenol administration.

*Currency rate in July 2004: 1 = US $1.215
**Currency rate in July 2004: 1 = GB £0.660
However, prostacyclin can cause hypotension as well. This complication is infrequent due to its fast metabolism and very short half-life (minutes). Furthermore, its low molecular weight (sodium epoprostenol 374.45 Dalton) and its low protein-binding fraction preclude a significant elimination by ultrafiltrate and dialysate fluids.

Knowledge of prostacyclin pharmacokinetics is difficult because of its instability. In rabbits its half-life was 2.7 minutes, the systemic clearance 93 mL·kg⁻¹·min⁻¹ and the whole body volume of distribution 357 ml·kg⁻¹ (13).

With regard to the reported experiences with epoprostenol as anticoagulant in CRRT, Journois et al administered PGI₂ associated with heparin in 11 patients resulting in a filter duration which was 55% higher than when only heparin was used (9). In a shorter series epoprostenol was used in 7 patients without heparin for 630 hours, their filter duration being 30% shorter than that with heparin, without bleeding complications (14). In a randomized controlled trial, Langenecker et al (15) found a filter duration of 14.3 hours with heparin, 18.8 hours with epoprostenol and 22 hours with the combination of these 2 drugs, in 12, 14 and 19 patients, respectively. Davenport et al (8) in a cross-over nonrandomized study on 17 patients suffering from renal and liver failure, prescribed epoprostenol as the only anticoagulant in 9 of them, reporting less bleeding than in 8 other patients treated with heparin alone. Six children were treated by Zobel et al (16) with epoprostenol under arteriovenous hemofiltration combined with low-dose heparin, without hemorrhagic or hemodynamic complications. PGI₂ has been used in combination with heparin by other authors in hemofiltration after heart surgery (17). Other prostaglandins, such as prostaglandin E₁, have been evaluated. Different dosages of prostaglandin E₁ (20 vs. 5 ng·kg⁻¹·min⁻¹) have been analyzed in combination with heparin without finding a different rate of bleeding (18). However, the authors also found that the higher the dose the longer the filter life-span (32 vs. 22 hours). Epoprostenol and prostaglandin E₁ were compared in a controlled randomized trial with 3 groups: heparin as a control group (17 patients) and either prostaglandin plus heparin in the others (15 with prostacyclin and 18 with PGE₁) resulting in a filter lifespan greater than 24 hours in 36%, 65% and 59% of them, respectively (19). The addition of prostaglandin E₁ or prostacyclin to unfractionated heparin inhibited platelet reactivity and aggregation during continuous hemofiltration in a dose-dependent way (15, 18, 19). By reducing PF4 release and associated heparin inactivation, prostaglandins act synergistically with unfractionated heparin (UFH). If the clotting tendency is increased, predilution reinfusion or the addition of prostaglandins to heparin may be helpful and has been recommended with grade C (supported by small randomized trial with high risk of false positive or false
negative error, and with fewer than 25 patients per group) in a recent article (20).

Due to the limitations of heparin, alternative anticoagulation strategies other than epoprostenol have been developed. Citrate anticoagulation has been documented to be an effective strategy for patients receiving CRRT (20-23). Limitations of citrate anticoagulation include the risks of hypocalcemia and metabolic alkalosis. Furthermore, its use requires intensive blood ionic Ca ++ monitoring and calcium-free dialysate. Hirudin, a direct thrombin inhibitor, is an effective anticoagulant and its use in CRRT has been proved (24). Its main drawbacks are the lack of an antidote and its excessively long half-life in renal failure. The sieving coefficient of hirudin ranks from 0.4 with an AN69 membrane to 0.6 with polysulphone (25). Argatroban, a synthetic arginine inhibitor, is approved for patients with heparin-induced thrombocytopenia. This agent is metabolized by the liver and not cleared by a dialysis membrane (4).

We propose an algorithm (Fig. 3) which may be helpful in deciding the strategy of circuit anticoagulation in CRRT.

The series we have reported in this article is the largest in hours of follow up and the second in number of patients after the Fiaccadori et al series (26). The main limitation of the present study is its uncontrolled and retrospective design. Epoprostenol may be safely used to prevent clotting of the extracorporeal circuits, either alone, in patients with thrombocytopenia and/or increased risk of bleeding, or in combination with heparin in states of hypercoagulability. Its high cost can in great part be compensated for by savings on fungibles and nurse time in re-changing filters.

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