Prostacyclin as an Anticoagulant for Continuous Renal Replacement Therapy in Children

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Keywords

Prostacyclin · Paediatrics · Continuous renal replacement therapy · Anticoagulation · Epoprostenol

Abstract

Effective delivery of continuous renal replacement therapy (CRRT) depends on the longevity of the filter and circuit used in the CRRT machine. Safe and effective anticoagulation is crucial for maintaining the patency of these circuits. In children, heparin and citrate are the commonly used anticoagulants but they are limited by serious side effects and thus calls for meticulous monitoring. In conditions where neither of these can be used, prostacyclin can be an effective alternative. Prostacyclin is a platelet inhibitor that can be safely used as an efficient anticoagulant in CRRT. When combined with heparin, it induces a heparin-sparing effect, which can reduce the dosage and side effects of heparin. Furthermore, there is no need for performing time-consuming monitoring tests. Although prostacyclin seems to be an attractive option, there is scanty evidence about its use as an anticoagulant in CRRT in children. We review the evidence and practicalities, and propose a guideline for the use of prostacyclin as an anticoagulant in children requiring CRRT.

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Introduction

Since 1984 when Claudio Ronco treated the first child with continuous arterio-venous haemofiltration (CAVH) in Vicenza in Italy, vessel-based renal dialysis has evolved from an acute lifesaving intervention to a long-term method of treatment. The modern approach to the treatment of acute kidney injury (AKI) emphasizes introducing continuous renal replacement therapy (CRRT) early in the course of disease in order to avoid complications to other organs [1].

Successful CRRT requires uninterrupted flow through these circuits. With the use of any extracorporeal circuit, anticoagulation becomes important to prevent circuit clotting. In the intensive care unit (ICU) setting, it is quite challenging to achieve a balance between prevention of circuit clotting using an anticoagulant versus the risk of bleeding due to the side effects of the anticoagulant used.

Among the various anticoagulants that have been tried for paediatric CRRT, heparin and citrate are the most widely used; however, each of these agents has its own limitations. In addition, there is limited data regarding the safety and efficacy of different methods of anticoagulation in these patients. Unfortunately, there is no evidence base to suggest the use of one particular anticoagulant over the other. One of the anticoagulants well de-

scribed in literature but not widely used is a prostaglandin derivative – prostacyclin.

This review will focus on the use of prostacyclin as an anticoagulant in paediatric CRRT.

Why Is Anticoagulation Important in CRRT?

Successful running of the CRRT circuit in critically ill children requires circuit longevity to minimize treatment downtimes. Premature circuit clotting not only leads to reduced clearance but also contributes to cardiovascular instability when coming on and off CRRT, increased blood loss, higher workload, and more expense. Therefore, improving circuit life is clinically relevant.

In normal haemostasis, the negatively charged membrane of the vascular endothelium maintains fluidity of the blood through a complex interaction between plasma proteins and platelets. With the use of an extracorporeal circuit, the fine balance shifts to a hyper-coagulant state when there is continuous contact between blood and the foreign surface of the membrane. As clotting factors, platelets and calcium are necessary to promote coagulation; agents that can antagonize any of these three components can work as an anticoagulant.

Circuits used in the paediatric population are more prone to clotting as children have a smaller blood volume, a higher relative surface area of the dialyzer, and small-bore vascular catheters. All these factors potentially increase contact activation of coagulation proteins, platelets, and inflammatory cells, predisposing to premature clotting.

Although there are various patient and treatment related factors that can be optimized to keep the circuits patent, use of an anticoagulant is a key factor to increase the filter life of these smaller circuits. Brophy et al. [2] looked at CRRT circuits in children anti-coagulated with either heparin, citrate or anticoagulant-free. They demonstrated that the mean circuit survival was not different for circuits receiving heparin anticoagulation (42.1 h) and citrate anticoagulation (44.7 h) but was significantly lower for circuits with no anticoagulation (27.2 ± 21.5 h). Kaplan–Meier analysis revealed no survival difference between heparin and citrate circuits but significantly lower survival for circuits where no anticoagulation was used. Log-rank analysis showed that 69% of heparin and citrate circuits compared to only 28% of anticoagulation-free circuits that were functional at 60 h. So it was clear that anticoagulation is necessary to prevent these circuits from clotting prematurely.

Coagulation – The New Model

The classic coagulation cascade, proposed in 1964 by Macfarlane, Davie and Ratnoff described 2 independent pathways: the extrinsic pathway and the intrinsic pathway [3, 4]. Platelets and calcium play a very important role in the progression of this cascade.

We all acknowledge that the classical intrinsic and extrinsic models of coagulation have inter-dependencies rather than operating as independent pathways [5]. Therefore, a new coagulation model was developed based on 3 interdependent processes of initiation, amplification and propagation.

The new coagulation model has thrombin at the center of the coagulation universe; production and breakdown of thrombin regulates all aspects of haemostasis. Once thrombin is formed, it can be directed along a variety of different pathways, which can result in diverse, clinically significant coagulation functions. There is a positive feedback from thrombin to generate more thrombin. In addition, thrombin participates in its own downregulation. As soon as clotting is initiated and thrombin is generated, it starts the upregulation and downregulation depending on the need. The coagulation cascade and platelets can both be targeted for use in the prevention of clotting in the extracorporeal circuit.

Common Anticoagulants Used in Paediatric CRRT

Although there is no consensus on the agent of choice for anticoagulation in CRRT, heparin and citrate are the most commonly used anticoagulants.

Heparin

In the United Kingdom, most of the paediatric centers offering CRRT use heparin as an anticoagulant. Unfractionated heparin (UFH) has its own advantages in terms of cost, familiarity of use, availability of point-of-care testing with activated clotting time (ACT), short half-life, and possible reversal with protamine. However, its use is limited by significant disadvantages, such as a propensity to cause haemorrhage, dosage variability, heparin resistance and the development of heparin-induced thrombocytopenia [6]. Its use is shown to be associated with a risk of bleeding that is seen in 4–30% of adult patients on CRRT [7, 8]. Since anti-thrombin III is the substrate on which heparin acts, it may not be the best choice in conditions where anti-thrombin III is depleted, such as severe sepsis or when there is evidence of disseminated intravascular coagulation.

ACT monitoring of heparinization has always been a matter of debate because of its extreme variability and absence of a correlation with plasma heparin levels.

Citrate

Calcium, an important co-factor in the progression of the clotting cascade, is chelated by the administration of pre-filter citrate. The associated regional hypocalcaemia in the filter inhibits the generation of thrombin. Therefore, regular monitoring of ionized calcium (iCa^{++}) concentration in the extracorporeal circuit is important to maintain adequate anticoagulation and it is suggested that ionized calcium level below 0.35 mmol/l is ideal [9]. Citrate is itself cleared by convection and diffusion and lost in the effluent; hence, meticulous monitoring of serum calcium levels and additional supplementation to the patient are required.

In addition, the citrate that passes into the circulation can cause metabolic alkalosis.

Various studies in children and adults have demonstrated better safety profile and filter life with the use of citrate when compared to heparin [10].

Just as the use of heparin can be a concern in those with bleeding abnormalities, citrate metabolism can be a concern in those with liver dysfunction. Use of citrate is not universal and requires very close monitoring of ionized calcium and acid–base balance. Of note, a citrate module is not available with all CRRT machines.

Other Anticoagulants

Neither heparin nor citrate anticoagulation provides a perfect solution for prolonging circuit longevity, and so the possibility of a safe and efficacious alternative CRRT anticoagulation agent remains an attractive prospect. Other anticoagulation methods for CRRT described in the literature with varying efficacy include regional heparinization, low molecular weight heparin, saline flushes, prostacyclin, nafamostat (serine proteinase inhibitor), hirudin, and regional citrate anticoagulation [11–17].

Prostacyclin is an effective anticoagulant that can be used in situations where heparin nor citrate cannot be used or may be ineffective, particularly in patients with coagulopathy as in liver failure.

Prostacyclin

Prostacyclin (also called prostaglandin I₂ or PGI₂) is a member of the family of lipid molecules called eicosanoids, synthesized from the arachidonic acid (AA)

pathway by cyclooxygenase enzymes. It is produced by endothelial cells of blood vessels. It is both a potent vasodilator and inhibitor of platelet aggregation. Epoprostenol, the synthetic equivalent of prostacyclin, is the drug currently used as an anticoagulant for paediatric CRRT.

History

The discovery of prostacyclin is linked to the work of two gynaecologists in 1930, when instillation of human semen into the uterus was found to cause uterine contraction or relaxation [18]. Since the source of the active ingredient was thought to be the prostrate, they were named ‘prostaglandins’.

This was followed by a period of quiescence and neglect until the 1970s when there was a resurgence of interest and an explosion of research, culminating in the award of the Nobel Prize for Medicine in 1982 to Bergström, Samuelsson and Vane, who were able to show that prostaglandins are involved in a diverse range of biochemical functions and processes.

In 1976, when searching for tissues other than platelets that would produce thromboxane A₂, Professor John Vane, an English pharmacologist under the leadership of Sir Salvador Moncada, a Honduran-British pharmacologist, identified a vasodilator substance they called PGX that had diametrically opposite effects to thromboxane A₂ and inhibited platelet aggregation. PGX, or prostacyclin, is now known to be the main product of AA in vascular tissue. The first research paper on prostacyclin was published in the scientific journal *Nature* in October 1976 [19].

The same team collaborated to produce a synthetic molecule called Epoprostenol. This was the first prostanoïd approved by FDA to treat pulmonary arterial hypertension (1995).

Pharmacological Properties

Prostacyclin (PGI₂) is a member of the prostaglandin family of bioactive lipids and is a derivative of AA (or 5,8,11,14-eicosatetraenoic acid) produced by vascular endothelial cells. Both cyclooxygenase enzymes (COX-1 and COX-2) convert AA into the prostaglandin precursor PGH₂, which is subsequently converted into prostacyclin (PGI₂) via prostacyclin synthase.

Prostacyclin is metabolised rapidly and has a very short half-life (42 s) [20]. It is rapidly inactivated to form 6-keto-prostaglandin F_{1α} [21]. Furthermore, its low molecular weight (sodium poprostenol 374.45 dalton) and low protein-binding fraction preclude significant elimination by ultra-filtrate and dialysate fluids. Pharmacokinetic studies are difficult because of its instability. In rabbits, its half-

life was noted to be 2.7 min, the systemic clearance 93 ml · kg⁻¹ · min⁻¹ and the whole body volume of distribution 357 ml · kg⁻¹ [22]. Prostacyclin acts as a potent vasodilator and is a major inhibitor of platelet aggregation [23]. PGI₂ also inhibits vascular smooth muscle cell proliferation and differentiation [24]. Prostacyclin has been extensively used as a pulmonary vasodilator in patients with pulmonary hypertension and in babies with persistent pulmonary hypertension of the newborn [25, 26].

In addition to beneficial effects of prostacyclin as an anticoagulant, it can potentially help to optimize oxygen delivery and uptake in critically ill patients [27]. This property of PGI₂ can be of advantage in critically ill children with multi-organ failure who are haemodynamically unstable.

Mechanism of Action

The actions of prostacyclin are mediated through a 7-transmembrane-spanning G-protein coupled receptor (GPCR), referred to as the IP receptor (International Union of Pharmacology nomenclature). GPCR mediates intracellular signalling via adenylyl cyclase activation and cyclic AMP (cAMP) production [28]. It exerts its anticoagulant effects through its anti-platelet effect. It also has a heparin-sparing effect, which can be crucial to prevent the side effects of higher doses of heparin.

Antiplatelet Effect

Contact of blood with the extracorporeal circuit results in platelet activation as evidenced by increased P-selectin expression on platelets. There is enhanced activation of polymorph nuclear cells as evidenced by increased CD11b expression and the formation of platelet-PMN aggregates. The formation of such heterotypic aggregates has been implicated in the pathophysiology of multi-organ failure, disseminated intravascular coagulation and thrombosis.

Platelet membrane GPIIb-IIIa complex is the functional fibrinogen receptor responsible for platelet aggregation [29]. Increased homotypic platelet aggregation induces haemofilter clotting and results in platelet consumption. P-selectin mediates interaction of platelets with monocytes and PMN, resulting in the formation of heterotypic aggregates. Prostacyclin reversibly inhibits platelet function and also reduces heterotypic platelet leucocyte aggregation during clinical haemofiltration in critically ill patients [30].

Platelet integrin Glycoprotein IIb-IIIa mediates the final common step of platelet activation by undergoing a conformational change, binding fibrinogen and Von Willebrand (VwF) factor leading to platelet aggregation

and formation of a fibrin-rich thrombus. Prostacyclin interferes in this process by inhibiting the Glycoprotein IIb-IIIa receptor, through adenylyl cyclase.

Prostacyclin activates adenylyl cyclase, leading to an increase in cAMP levels. cAMP mediates phosphorylation of vasodilator stimulated phosphoprotein (VASP) to phosphorylated form (VASP-P), which inhibits glycoprotein IIb-IIIa receptor activation, thereby inhibiting platelet aggregation and finally the process of thrombus formation (fig. 1).

Elevation of platelet cyclic nucleotides interferes with all known platelet activatory signalling pathways and thus blocks cytoskeletal rearrangement, fibrinogen receptor activation, degranulation, and expression of pro-inflammatory mediators.

Arcangeli et al. [31] have compared platelet function and anticoagulation strategies – UFH versus prostacyclin – in patients undergoing continuous veno-venous haemodiafiltration. In the heparin group, platelet responsiveness to collagen was significantly increased by 30% in post- vs. pre-filter samples. This effect was seen to be blunted in the prostacyclin group. Thus, it was clear that heparin did not protect platelets from filter-induced activation and was associated with a reduced function of systemic platelets. Prostacyclin, on the other hand, protected the platelets against the activatory effect of the filter [27].

Heparin-Sparing Effect

Prostacyclin can significantly reduce the amount of heparin needed for effective anticoagulation – probably because of the reduced inhibition of UFH by platelet factor 4 (fig. 2).

Platelet factor-4 (a low molecular weight protein) released from the alpha-granules of activated platelets binds to heparin with high affinity. It mainly acts by the neutralization of heparin-like molecules on the endothelial surface of blood vessels, thereby inhibiting local antithrombin III activity and promoting coagulation. It has been shown that prostacyclin can inhibit the release of platelet factor 4 by 85–95% [32]. Therefore, the same amount of anticoagulation can be achieved by using lower doses of heparin when prostacyclin is added to heparin.

The powerful platelet-preserving and heparin-sparing effects of prostacyclin were first demonstrated in animal experiments in 1978 [33]. Subsequent studies in humans have confirmed similar effects. Turney et al. [34] have shown that prostacyclin can also prolong the half-life of heparin by up to 40%.

Herrera-Gutiérrez et al. [35] have reported the use of epoprostenol and UFH either in isolation or combined as

Fig. 1. Cell-based model of coagulation. **a** Initiation phase. This phase occurs on the TF-bearing cell, when injury exposes these cells to the flowing blood. It results in the generation of a small amount of FIXa and thrombin that diffuse away from the surface of the TF-bearing cell to the platelet. **b** Amplification phase. In the second phase, the small amount of thrombin generated on the TF-bearing cell activates platelets, releases VwF and leads to the gen-

eration of activated forms of FV, FVIII, and FXI. **c** Propagation phase. In the third phase, the various enzymes generated in earlier phases assemble on the pro-coagulant membrane surface of the activated platelet to form intrinsic tenase complex, resulting in FXa generation on the platelet surface. This results in a burst of thrombin generation directly on the platelet and formation of fibrin. TF = Tissue factor.

an anticoagulant to maintain circuit patency. Epoprostenol was used in patients at risk of bleeding; it was combined with heparin for use in those with problems of early coagulation of the filters. While epoprostenol, when used in isolation provided a similar duration of circuit life compared to UFH, it had far less bleeding complications. However, when epoprostenol was combined with heparin, the circuit life almost doubled, with half the dosage of heparin.

Side Effects

Due to its short half-life, complications of prostacyclin are minimal. The main side effect described is hypotension due to vasodilatation. This complication usually responds to intravascular volume expansion with fluids, addition or increase in the dose of vasopressors, or decrease in the dosage of prostacyclin. There might be an increased

incidence of bleeding in patients with oesophageal varices due to the inhibition of platelets and increased blood flow in the portal venous system. In fulminant hepatic failure, minimal increase in ICP has been reported. Systemic side effects (hypotension, and an increase of intracranial pressure) can be further prevented or limited by infusion into the extracorporeal circuit, reducing the systemic levels due to extracorporeal elimination [36].

Other rare dose-limiting adverse events with the use of prostacyclin (occurring in <1% of patients) include nausea, vomiting, headache, hypotension, flushing, chest pain, anxiety, dizziness, bradycardia, dyspnoea, abdominal pain and tachycardia, although these are mainly described in adults who are not on CRRT.

Prostacyclin can also cause ventilation perfusion mismatch with an increase in alveolar–arterial oxygen ten-

Fig. 2. Antiplatelet effect of prostacyclin. Prostacyclin acts through G-protein coupled receptor resulting in increased C-AMP, which mediates conversion of VASP to VASP-P, which inhibits Glycoprotein IIb–IIIa receptor activation, thereby inhibiting platelet ag-

gregation and thrombus generation cAMP. c-AMP = Cyclic adenosine monophosphate; VASP = vasodilator-stimulated phosphoprotein; VASP-P = phosphorylated vasodilator stimulated phospho-protein.

sion gradient. This might be clinically significant in those with reflex hypoxic pulmonary vasoconstriction [37].

The clinical effects of epoprostenol (synthetic equivalent of prostacyclin) are summarized in table 1.

Gainza et al. [38] studied 38 adult patients undergoing CRRT using prostacyclin and reported haemorrhage and a fall in blood pressure (both approximately 18%), which recovered within 24 h after treatment was initiated.

Safety of intravenous prostacyclin has also been demonstrated in neonates receiving this drug for severe pulmonary hypertension [39]. Prostacyclin is, therefore, a safe drug when used as an anticoagulant (either regionally in the CRRT circuit or intravenously).

Marketing

Epoprostenol is marketed as Flolan® (GlaxoSmith-Kline plc, London, UK) and is also available as a generic (Teva Pharmaceutical Industries Ltd., Petah Tikva,

Israel). Since 2008, a room-temperature stable formulation of epoprostenol (Veletri®, Action Pharmaceuticals Ltd., Allschwil, Switzerland) has also been available.

Evidence for Use of Prostacyclin for CRRT in Children

Prostacyclin has been commonly used for treating pulmonary hypertension in children, but its use in paediatric CRRT has been limited. The literature search on prostacyclin in paediatric CRRT is rather frustrating with mainly case series and observational studies.

We performed a literature review using the PubMed, Medline, Embase and Cochrane databases with the search/MESH criteria ‘prostacyclin, epoprostenol, renal replacement therapy, haemofiltration in children 0–18.’ Detailed literature review since 1990 revealed few studies using prostacyclin in paediatric CRRT. There have been

Table 1. Clinical effects of epoprostenol (synthetic equivalent of prostacyclin)

Major actions	(1) Inhibition of platelet aggregation thus preventing formation of platelet plug (2) Direct vasodilation of pulmonary and systemic arterial vascular beds [49]
Possible adverse events	(1) Bleeding from oesophageal varices (2) Ventilation perfusion mismatch
Other actions (mainly observed in animals)	(1) Increase in cardiac index and stroke volume – dose related (2) Decrease in pulmonary vascular resistance and mean systemic arterial pressure – dose related (3) Effect on heart rate – vagally mediated bradycardia in low doses and reflex tachycardia at higher doses (because of hypotension) (4) Anti-proliferative effects on the intimal layer of pre-capillary arteries [50] (5) Bronchodilation, inhibition of gastric acid secretion, decreased gastric emptying
Toxicity (extension of dose-limiting effects)	Flushing, headache, hypotension, nausea, vomiting, diarrhoea, anxiety, dizziness, chest pain, dyspnoea, bradycardia, tachycardia
Acute toxicity (noted in mice and rats)	Mainly ataxia, hypoactivity, loss of righting reflex, deep slow breathing, and hypothermia [51]
Lethal dose (mice)	Single intravenous dose of 10 mg/kg [51]

no randomized control trials in children to date comparing prostacyclin and other commonly used anticoagulants for CRRT.

Use of prostacyclin as an anticoagulant is described in adults with AKI. Most of the studies were conducted whenever heparin was contraindicated or caused side effects.

We have used prostacyclin safely and effectively in critically ill patients with both liver and non-liver problems. Use of an anticoagulant in patients with liver failure is always a topic of debate. Clinicians are hesitant to use any anticoagulation due to abnormal clotting tests and perceived risk of bleeding. In fact, most of these patients are pro-coagulant and require anticoagulation [40].

Our group from King's College Hospital, London (Goonasekera et al. [41]) recently reported the use of prostacyclin as an anticoagulant in 62 filtration episodes in children with acute liver failure and abnormal clotting results. The mean duration of circuit use was 53 h with no reported complications due to its use. Although citrate has been said to be contraindicated in patients with liver failure, Caroline S demonstrated that while citrate accumulates in patients with liver failure, incidence of citrate toxicity remains low, and depends on the severity of liver failure as measured by prothrombin time and lactate at initiation of CRRT [42].

Zobel et al. [43] had earlier reported to have used prostacyclin either alone or with heparin in 6 children with pre-existing coagulopathy and high risk of bleeding.

There was an approximately 20% increase in filter life in the heparin/prostacyclin combined group compared to heparin alone. No adverse events were reported.

Zobel et al. [44] have also reported the use of prostacyclin for CAVH in 5 critically ill premature infants with a mean gestational age of 31.8 ± 3.8 weeks. Prostacyclin was the sole anticoagulant (dose of 5–10 ng/kg/min) in 4, with concomitant heparin and prostacyclin in one. The filter life was 14 h, with no reported side effects due to prostacyclin. This is the earliest report of the use of prostacyclin in premature infants.

Langenecker et al. [45] evaluated 46 critically ill adults on continuous veno-venous haemofiltration (CVVH) who had been randomized into 3 groups – group 1: heparin, group 2: prostacyclin, and group 3: heparin and prostacyclin. Filter life, haemostatic and haemodynamic variables were evaluated at various time intervals. It was seen that filter life was the longest (22 ± 0.9 h) in the combined heparin and prostacyclin group compared to other groups. In addition, patients receiving both prostacyclin and heparin showed better haemodynamic profiles compared with other groups and no bleeding complications were observed. The dose of heparin and prostacyclin used in this group was 5 ± 0.4 IU/kg/h and 6.4 ± 0.3 ng/kg/min respectively.

In another prospective randomized controlled trial, regional anticoagulation of pre-filter heparin and post-filter protamine combined with pre-filter prostacyclin (group 1) was compared with systemic heparin (group 2)

Table 2. Summary of relevant studies using prostacyclin as an anticoagulant for CRRT

Reference	Age group	Patient/circuits characteristics	Dosage	Results	Comments
Goonasekera et al. [41], 2015	0–18 years	62 filtration episodes. Liver dysfunction	Prostacyclin: 4 ng/kg/min	Mean duration of circuit use – 53 h	No reported complications
Zobel et al. [43], 1988	6 children (10 days to 12 years)	Preexisting coagulopathy/thrombocytopenia	Prostacyclin as sole or with heparin	20% increase in filter life when prostacyclin was added	No adverse events reported
Zobel et al. [44], 1989	5 preterm infants 31.8 ± 3.8 weeks	Mean duration of CAVH 53.6 ± 14 h	Prostacyclin: 5–10 ng/kg/min	Mean circuit use – 14 h	No side effects observed
Langenecker et al. [45], 1994	Adults	3 groups Gr 1: UFH (n = 13) Gr 2: PGI2 (n = 14) Gr3: UFH+ PGI2 (n = 19) Critically ill on CVVH	Prostacyclin alone: 7.7 ± 0.7 ng/kg/min. With heparin 6.4 ± 0.3 ng	Circuit life longest when prostacyclin + heparin (22 h)	Better hemodynamic profiles. No bleeding complications
Gainza et al. [38], 2006	Adult	38 patients	Prostacyclin: 5 ng/kg/min	Circuit life increased by 50%	Bleeding (18%) Fall in BP (18%) Recovered in 24 h
Fabbri et al. [46], 2010	Adult prospective RCT	90 patients Critically ill patients with ARF UFH + PGI2 (n = 46) vs. UFH (n = 44)	Prostacyclin: 4 ng/kg/min	Circuit life- 68 vs. 19 h	Platelets reduced progressively while on heparin alone
Balik et al. [52], 2005	Adult Compared with citrate as an alternative coagulant	32 patients UFH + PGI2 (n = 17) vs. Citrate (n = 15)	Prostacyclin: 4–10 ng/kg/min	Circuit life 26 vs. 36.5 h	Hypotension 23% in 1st gp. Increased dose of PGI2 does not increase hemodynamic side effects
Herrera-Gutiérrez et al. [35], 2006	Adult	389 patients. Prostacyclin used in those with risk of bleeding. Combined with UFH – when issues with early clotting of filters	Prostacyclin: 4–5 ng/kg/min either when isolated or when combined with UFH	Circuit life almost doubled when combined with UFH (27 h)	Mild bleeding in 3% patients
Fiaccadori et al. [47], 2007	Adult (SLED)	35 patients. Also prostacyclin given directly to patient: 1/2 dose	Prostacyclin: 6 ng/kg/min	90% sessions completed as prescribed	No increase in risk of bleeding

in critically ill adult patients with acute renal failure undergoing CRRT. Fabbri et al. [46] found that the median filter life span using regional anticoagulation with prostacyclin was more than three times that of systemic heparin alone. Transmembrane pressure remained unchanged in group 1, while it increased up to 3 times in group 2. The platelet count remained stable in group 1, while it decreased progressively in group 2.

Although these studies were mainly conducted in adult patients, children with a similar pathophysiology could have similar results. However, further studies in children are necessary. Some of the relevant studies are summarized in table 2.

In addition to CRRT, prostacyclin has also been used as an anticoagulant in sustained low-efficiency dialysis (SLED). In this study of 35 critically ill patients with acute renal failure treated with SLED, the authors looked at the safety and efficacy profile of prostacyclin and found that the number of sessions that had to be interrupted because of circuit clots was decreased when compared with their standard treatment of saline flushes. Hypotension and bleeding profile were the same. Changes in systolic blood pressure and heart rate from baseline during SLED, and over the following 6 h post procedure, were not significant. The authors, therefore, concluded that prostacyclin was a safe and effective anti-haemostatic agent for SLED [47].

Guidelines for Use of Prostacyclin (Epoprostenol) in Children on CRRT

We propose the following protocol for the use of prostacyclin as an anticoagulant in CRRT. This protocol is being used in the PICU of King's College Hospital, London.

Method of Administration

Due to its short-half life, epoprostenol is used as a continuous infusion into the extracorporeal circuit. The infusion should be stopped when CRRT is discontinued. Epoprostenol has a vasodilatory effect at 20 ng/kg/min and an antiplatelet effect at 2–8 ng/kg/min.

Making Up the Infusion

Epoprostenol is available either as a 0.5 or a 1.5 mg glass vial. Following the manufacturer's recommendation for reconstitution, each ml of the reconstituted drug contains 10 µg of epoprostenol. Then 12 µg/kg (1.2 ml/kg) of the reconstituted drug is diluted in 0.9% normal saline to make up to 50 millilitre solution. The reconstituted solution should be discarded after 12 h. If both prostacyclin and heparin are used together, prostacyclin is administered via the CRRT machine attached to the pre-filter access port, whereas heparin is given via an infusion pump connected by a 3-way tap before prostacyclin enters the pre-filter port. It is advisable not to bolus or flush the anti-coagulant line with prostacyclin, as it has a potential to cause a severe drop in blood pressure.

Dosage

The infusion is started at 4 ng/kg/min. If the filter life is less than 48 h, the dose is increased by 2 ng/kg/min to a maximum of 8 ng/kg/min, watching closely for side effects.

Infusion Rate

The above infusion is run at 0.5–2 ml/h, for targeted drug delivery between 2 and 8 ng/kg/min.

Monitoring

Prostacyclin use for paediatric CRRT does not need complex monitoring. Side-effects such as bleeding and systemic haemodynamics can be monitored clinically. Further monitoring with platelet function tests can be done but incurring additional costs and results are not readily available. These tests are not routinely employed in clinical practice. Thromboelastography or Rotational Thromboelastometry may be useful.

Cost Effectiveness

Cost can be an important factor to consider while using prostacyclin as an anticoagulant. However, when one takes into account the cost of changing clotted filters and circuits, including monitoring costs with other anticoagulants, the overall cost of using prostacyclin might be less.

An average 10 kg child on CRRT using prostacyclin as the sole anticoagulant will need 50 µg/day (considering 4 ng/kg/min infusions). Currently, smaller vials are not available, thus forcing the use of a larger vial and incurring more cost. For the same patient on heparin as the sole anticoagulant (with infusion of 30 IU/kg/h), the cost would be approximately £3 per day. Considering the price of the frequent point-of-care and laboratory testing required, blood loss, nursing times and the need for more frequent filter change, prostacyclin might be a more cost-effective option. Cost analysis in one study has demonstrated the advantage of using prostacyclin (versus heparin) in patients with an increased tendency to clotting [32].

Personal Experience with Using Prostacyclin as Anticoagulant for Paediatric CRRT in the PICU of King's College Hospital, London

At King's College Hospital, prostacyclin is used as the first-line anticoagulant – either as a sole anti-haemostatic agent or occasionally in combination with heparin.

We have retrospectively looked into our experience of using prostacyclin as a sole anticoagulant in all children who received CRRT in the 16-bedded PICU over a 7-year period. Patients were stratified according to their liver disease (LD) status and the anticoagulant used – heparin, prostacyclin or no anticoagulant. Efficacy was measured by filter life and mortality. Safety was assessed by the number of bleeding episodes per 1,000 h of CRRT, use of blood products (RBC, FFP or platelets) and number of hypotensive episodes requiring a therapeutic intervention (fluids/vasopressors) during CRRT.

In this unpublished data from our hospital, more than 100 children requiring CRRT were studied. The LD and non-LD (NLD) groups were comparable with regard to the severity of the disease as assessed by the Paediatric Index of Mortality score. NLD patients included those with septic shock, crush injury, fluid overload, and hyperthermia. The median duration of filter life increased from 28 to 53 h and 34–56 h during prostacyclin use when compared with heparin in LD and NLD children respectively.

Comparing prostacyclin with heparin (used as sole agents), the risk of bleeding and use of blood products

was higher in both the LD and NLD groups with the use of heparin. The relative risk of bleeding was 5–7 fold higher with heparin when compared to prostacyclin. There was no increase in the incidence of hypotension with the use of prostacyclin. We have found that prostacyclin used as a sole anti-haemostatic agent increases filter life and decreases bleeding risk without increasing platelet consumption, hypotensive episodes or mortality. Therefore, we currently use prostacyclin as a first-line anticoagulant in patients with both liver and NLDs undergoing CRRT due to its efficacy, safety profile and uncomplicated monitoring. We have not found an increase in the incidence of hypotension or decreased platelet count leading to clinically evident bleeding even in patients with septic shock on vasopressors and inotropes.

Another important pharmacologic property of prostacyclin is the heparin-sparing effect which can be effectively used in patients requiring escalating doses of heparin to achieve the desired ACT, and in those where filters/circuits clot frequently, for example, in patients who are extremely sick and septic with low AT-III. Using heparin alone in these patients may require escalating doses to achieve the same anticoagulation effect. Therefore, we use this combination quite commonly in our institute. Prostacyclin, by its anti-platelet and heparin-sparing effects, increases ACT and helps maintain longer filter life. We attach a 3-way tap and combine the two anticoagulants for the desired effect.

It is important to ascertain whether the antiplatelet effect of prostacyclin is dose dependent because there is a fear that higher doses might lead to more systemic side effects, especially hypotension. Kozek-Langenecker et al. [48] have studied various doses of prostaglandin combined with low doses of heparin on haemofilter life in 24 critically ill patients undergoing continuous CVVH. The

patients were anticoagulated with either 5 ng/kg/min PGE1 and 6 IU/kg/h heparin or 20 ng/kg/min PGE1 and 6 IU/kg/h heparin. Haemofilter life was significantly longer in patients anticoagulated with 20 ng/kg/min, PGE1 (32 ± 3 h) than with 5 ng/kg/min, PGE1 (22 ± 3 h), although in vitro bleeding parameters were significantly prolonged in post-filter blood in patients receiving 20 ng/kg/min, PGE1. Platelet counts remained stable.

Historically we had been using prostacyclin at 2 ng/kg/min, but we have changed our protocol recently to start at 4 ng/kg/min to go up in steps of 2–8 ng/kg/min. With this change, we have observed an increase in the duration of filter life without seeing any additional side effects.

Conclusion

Prostacyclin (epoprostenol) can be an effective alternative anticoagulant either alone or in conjunction with heparin for paediatric CRRT. It can be safely used in patients with thrombocytopenia and/or increased risk of bleeding both in patients with liver and non-liver disorders. Although heparin and citrate are the most commonly used anticoagulants, prostacyclin is an attractive alternative, with a favourable safety and efficacy profile. While the protocol and the safety profile have been promising, more research, particularly among children, is necessary for prostacyclin to be accepted as a universal add-on or sole anticoagulant.

Disclosure Statement

The authors declare no conflicts of interest.

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