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Original Article

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Sustained low-efficiency dialysis (SLED) with prostacyclin in critically ill patients with acute renal failure*

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Abstract

Background. Prostacyclin is an easy-to-use and safe antihaemostatic drug for continuous renal replacement therapies (RRTs). No study has been performed so far about its use in critically ill patients with acute renal failure (ARF) treated with sustained low-efficiency dialysis (SLED), a hybrid modality between conventional intermittent and continuous RRTs.

Methods. We studied 35 consecutive ICU patients with ARF, in whom data on safety and efficacy were prospectively collected in a single-centre experience over 15 months since August 2001. There were 25 males and 10 females; mean age, 72.1 (SD 11.4); mean APACHE II score at ICU admission, 24 (range 14–43); at RRT start, 27.4 (20–43); 28 patients (80%) were on mechanical ventilation and 17 (48.6%) had sepsis. SLED was performed using a conventional dialysis machine, with blood flow at 200 ml/min, bicarbonate-based ultrapure dialysate running at 100 ml/min, dialysate temperature 35°C and low-flux polysulfone filters. Prostacyclin, under the form of its synthetic analogue epoprostenol, was infused at 6 ng/kg/min before the filter.

Results. Out of 185 daily sessions performed (8–10 h, median 4 per patient, range 1–19), 19 (in 11 patients) were prematurely interrupted (10.3%; 95% CI: 5.4–18.6), after an average 58.5% of the prescribed treatment time (nine sessions in six patients for circuit clotting). This finding compared favourably with the experience we had at our unit using SLED with saline flushes. With the use of prostacyclin, two episodes of upper gastrointestinal bleeding were observed in 2/35 patients during SLED (5.7%; 95% CI: 0.7–19.2), corresponding to 1.1 episodes per 100 person-day on SLED. Therapeutic intervention for hypotension (fluids and/or vasopressor increase) was required in 45/185 (in 20 patients) of the sessions monitored (24.3%; 95% CI: 17.4–32.9); two sessions had to be interrupted because of refractory hypotension. Urea reduction ratio was 0.50 (SD 0.12); mean prescribed and obtained net ultrafiltration were 1.961 (range 0.5–5.0) and 1.991 (0.5–5.0), respectively. In-hospital mortality was 46%; mortality predicted by the APACHE II model at ICU admission was 42%; at SLED start, 51%.

Conclusions. Prostacyclin is a safe and effective antihaemostatic agent for SLED.

Keywords: acute kidney failure; critical illness; epoprostenol; intensive care unit; prostacyclin; SLED; sustained low-efficiency dialysis

Introduction

The range of available options for renal replacement therapies (RRTs) in critically ill patients with acute renal failure (ARF) has been recently extended with the introduction of prolonged, intermittent modalities in the intensive care unit (ICU) setting [1–7].

Such RRT modalities are indicated in the literature with different terms such as 'sustained low efficiency dialysis' (SLED), 'extended daily dialysis' (EDD), or 'slow continuous dialysis' (SCD), which substantially share the common operational characteristics of being run with low blood and dialysate flows (both typically ranging from 100 to 300 ml/min), and a relatively long duration (8–12 h a day); these RRT modalities can be implemented by using either commonly available machines for continuous RRTs (CRRTs), or standard dialysis machinery, filters, extracorporeal circuits and on-line-produced ultrapure dialysate [1–7].

The theoretical attractiveness of such RRT modalities derives from their combining the advantages of

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either the continuous or the conventional intermittent forms of RRTs [8]. On the one hand, they are associated with good tolerance to fluid ultrafiltration, narrow osmotic fluctuations, excellent azotaemia and solute control, and high flexibility in delivering nutritional support; on the other hand, they are characterized by procedural simplicity, low cost due to standard dialysis machine use and on-line dialysate production, and flexible scheduling [5–8]. Finally, as they are intentionally delivered as intermittent, though prolonged, treatments, it is likely that 'down-time' problems peculiar to CRRT modalities [9] should be less influent on the delivery of the prescribed dialysis dose.

Like CRRTs, anticoagulation of the extracorporeal circulation represents a crucial problem also in 'hybrid' techniques. In fact, the reported incidence of circuit clotting with SLED is 17–26% with heparin use, and 26–46% without any antihaemostatic agent use [1–3,5].

The optimal antihaemostatic strategy for RRTs is still a matter of debate, no consensus having been reached so far about this issue [10]. In the case of SLED, several strategies for maintenance of circuit viability have been proposed, such as saline flushes without antihaemostatic agents [1–3,5], unfractioned heparin [1,2,4,5] or citrate [11–13].

Prostacyclin is a physiological product of human endothelium with antiaggregant effects at low doses and vasodilatory effects at higher doses [14], which is available for clinical use as its synthetic analogue, epoprostenol. Prostacyclin inhibits platelet activation and aggregation induced by contact of platelets with the surfaces of the extracorporeal circuit during continuous haemofiltration [15]. Compared with other antihaemostatic drugs for RRTs, prostacyclin is easy to use and exerts an action that, due to its short half-life [14,16], fades away very rapidly after administration withdrawal. Prostacyclin has been used in various CRRT modalities [16–20], but never in SLED. The major concern regarding its safety is the hypotensive effect; however, to our knowledge, no study published so far has reported detailed data on blood pressure monitoring during RRT with prostacyclin.

Here we report the results of prostacyclin use in a consecutive series of 35 critically ill patients with ARF undergoing SLED over a 15-month period at our ICU. We prospectively collected data on prostacyclin use during 185 SLED sessions regarding indicators of both safety (incidence of bleeding complications, platelet consumption, changes in blood pressure, number of SLED sessions complicated by hypotension requiring therapeutic intervention) and efficacy (the ratio between effected and scheduled treatments, i.e. prescribed and delivered time of treatment, prescribed and delivered ultrafiltration, as well as the urea reduction ratio). As time for treatment is consistently shorter in SLED than in CRRT, a close correspondence between delivered and prescribed hours of treatment should be targeted; for this reason, we used prostacyclin doses which were 50% higher than those used in a previous study performed in patients on CRRTs [16].

Subjects and methods

Patients

Starting from August 2001, in our ICU, we replaced continuous venovenous haemofiltration (CVVH) with SLED as the preferred RRT modality for critically ill patients with ARF. Since we had been using prostacyclin as the antihaemostatic agent for CVVH, we went on using this drug for every SLED treatment until October 2002. Therefore, we included in the present study, all patients with a diagnosis of ARF consecutively admitted to our ICU during the time period August 2001–October 2002, who had been treated with SLED. Although we had not previously planned to do so, we also collected data from a series of patients admitted from November 2002–December 2005, in whom SLED was performed without using any antihaemostatic agent (hourly saline flushes only).

At our institution, the indication for prolonged modalities of RRTs is represented by the presence of at least two of the following features: intolerance to previous conventional treatment (intermittent haemodialysis) defined as intradialytic hypotension unresponsive to increased vasoactive drug support and/or fluids, hypotension or severe haemodynamic instability before RRT start (use of at least two vasoactive drugs), severe fluid overload (an estimated or measured fluid excess of >10% of actual body weight at the time of RRT initiation), severe catabolism (a daily increase in blood urea nitrogen of 50 mg/dl or more). SLED was started at the discretion of the attending nephrologist either as the first RRT modality, or after switching from previous intermittent daily dialysis; in the case of clinical status improvement, patients were usually returned to conventional haemodialysis. Our ICU is a closed, six-bed specialty unit for adult ARF patients with a bed to nurse ratio of 3:1. It is staffed by nephrologists with critical care expertise.

SLED procedure and antihaemostatic technique

Angioaccess was established by insertion of double or triple lumen 11.5–13.5 F central venous catheters into the internal jugular, subclavian or femoral veins. Patients were started on SLED with a blood flow of 200 ml/min and a dialysate flow of 100 ml/min on an AK200S Ultra type 1 machine (Gambro, Felino, Italy) with standard lines. No adjustements or modifications to machine software or hardware were needed. On-line ultrapure bicarbonate dialysate was generated by the bicarbonate AK200S Ultra proportioning system. Default dialysate composition was sodium 140 mEq/l, bicarbonate 34 mEq/l, K 4.0 mEq/l, Ca^{2+} 2.5 mEq/l; only in one case was K of 3.0 mEq/l utilized. The minimum dialysate flow of the AK200S machine in haemodialysis mode is 300 ml/min. To obtain a dialysate flow of 100 ml/min, we used the machine in the haemofiltration mode, setting the usual dialysate flow to zero, and in its place running the on-line replacement fluid at a slower rate countercurrent through the filter.

Polysulfone F7HPS filters with a Kuf of 9.8 ml/mmHg/h (Fresenius Italia, Italy) were used. Filters were primed with

21 of saline containing 5000 U/l of unfractioned heparin before the start of each SLED period. Daily treatments of 8–10 h duration were prescribed at the discretion of the attending physician. In most cases, SLED was run in the afternoon or over night.

We used prostacyclin as the sole antihaemostatic agent for SLED in all patients. Prostacyclin, as its synthetic analogue epoprostenol (Flolan, GlaxoSmithKline Italia, Verona, Italy), was prepared as indicated by the manufacturer (0.5 mg in 50 ml), then diluted to 500 ml of normal saline with the final solution containing 1 mcg/ml, which was infused into the circuit line (pre-filter) at the rate of 6 ng/kg/min. In order to ensure a full antiaggregant effect of prostacyclin, we infused the drug directly into the patient's central venous line for 15 min at the rate of 3 ng/kg/min immediately before connecting the patient to the SLED circuit. We adopted the strategy of pre-infusing directly into the patient, half the dose calculated for the circuit to make allowance for the fraction of the drug (about 50%) becoming unavailable to the patient [16,18] because of its loss by ultrafiltration and membrane adsorption. No monitoring of coagulation was routinely performed other than that required by the clinical conditions of the patient

Data collection

We extracted relevant data from the treatment data sheets routinely filled in by nurses and doctors, the clinical charts and the ARF database utilized in our unit since January 1994. Data regarding SLED monitoring were extracted by treatment data sheets routinely filled in by nurses and doctors. The following data were collected for each SLED with prostacyclin: date and hour of SLED start and end, filter type, dialysate potassium, prescribed and actual duration of the treatment, prescribed and obtained fluid balance goal, use of vasoactive drugs and/or initiation and/or dose increase, fluid and/or colloid administration for haemodynamic problems, duration of each session and reason for interruption, amount of blood restituted to the patient at the end of each SLED sessions (as total restitution, partial restitution, no restitution), haemorrhagic complications. Patient weight, arterial blood pressure, heart rate, fluid balance, circuit pressures (pre-filter, post-filter and ultrafiltrate/dialysate compartment) and transmembrane pressure (TMP) were monitored at least hourly during treatment; moreover, blood pressure and heart rate values were also collected from monitoring the sheets hourly from 6 h before to 6 h after SLED. Clinical and laboratory data, including the use of low-molecular-weight heparin (LMWH) as thromboprophylaxis, were also extracted from clinical charts. Prothrombin activity and activated partial thromboplastin time (aPTT) were obtained at SLED start and, subsequently, as required by the clinical course of the patients. Platelet count and laboratory data were collected daily.

Demographic and clinical data (such as diagnosis, ARF aetiology, acute and chronic comorbidities, complications, etc.) were already recorded in the prospective ARF database as a part of a study program aimed at evaluating the usefulness of severity of illness scoring systems, as well as complications and prognostic indicators of death in ARF patients [21–23]. For each patient, the Acute Physiology and Chronic Health Evaluation score in version II was calculated both at ICU admission and at SLED start [22,24,25].

In Italy, prostacyclin has been approved for use as antihaemostatic agent for RRTs since December 1992, its utilization being covered by the National Health System. SLED is a standard RRT modality in our unit. Approval from the Ethics Committee of the Parma University Medical School was obtained for the use of data already collected for clinical purposes.

Safety measures

We evaluated safety on the basis of the incidence of clinically important bleeding episodes, and the haemodynamic tolerance during RRTs. All bleeding episodes actually occurring during the SLED sessions or in the ensuing 72 h were considered haemorrhagic complications of treatment. We measured platelet consumption as the change in platelet count at the end of each SLED session, and analysed platelet count over all the days of the SLED treatments. Clinically important bleeding was defined as overt bleeding leading to either hypotension or transfusion of at least two packed red cells [23]. Haemodynamic stability was evaluated in two different ways: (i) The number of SLED sessions complicated by at least one hypotensive episode requiring therapeutic intervention (use of saline or colloid infusion, or initiation/increase of vasopressor support). We defined the hypotensive episode as a decrease in systolic blood pressure of 10 mmHg or more from an initial blood pressure of <100 mmHg or a decrease to <100 mmHg from an initial systolic blood pressure of 100 mmHg or more. (ii) The change in arterial blood pressure during the treatment with respect to the pre- and post-treatment values. In each patient, the haemodynamic stability during the SLED sessions was compared with that recorded during the intervals between SLED sessions. Data on platelet consumption and haemodynamic tolerance to SLED treatment were not available in the series of patients in whom SLED was performed with saline flushes.

Efficacy measures

We measured efficacy as the ratio of prematurely interrupted to scheduled treatments, the percentage of prescribed treatment time actually delivered and the percentage of blood restitution at the end of each SLED session. Reasons for session interruption were usually represented by unexpected clotting of the filter and/or the lines, or by an increase in TMP (i.e. the pressure gradient across the filter membrane) exceeding the maximum value recommended by the filter manufacturer. In some cases, interruptions were due to urgent out-of-unit procedures or diagnostic tests, or due to impending death of the patient. After each circuit discontinuation, blood restitution was recorded by the nurses as total, partial or not possible. Blood urea clearance, the sieving coefficient for urea and the urea reduction ratio were calculated according to standard methods [26]. The latter data were not available for SLED sessions performed with saline flushes.

Data analysis

To account for the presence of unbalanced and missing data, we used mixed-models repeated-measures linear regression analysis. In fact, number and duration of SLED sessions differed between patients, and data on the 10th, or 9th

and 10th h of treatment were missing for SLED sessions lasting 9 or 8 h, respectively. The number of platelet count ranged as widely as 1–19 per patient, being four on average. In the analysis of the changes in systolic and diastolic blood pressures and heart rate during SLED, patients were treated as random effects, while SLED treatment, vasopressor use and time points (h) were treated as fixed effects. We assumed a first-order autoregressive correlation structure in which observations closer together in time are more correlated than those further apart [27,28]. In this analysis, baseline values were taken as the average of the six hourly measurements preceding the start of each SLED session. We estimated the daily percent change of platelet count by fitting a random coefficients model (i.e. a model for linear time trend that allows the intercept and slope to vary randomly between patients) [27,28] after log-transformation of platelet count.

We expressed the frequency of haemorrhagic complications as the cumulative incidence to the first episode of bleeding. In addition, we measured the proportion of SLED sessions complicated by hypotension. The 95% confidence interval (CI), as well as the *P*-value for the comparison of the premature interruption of the SLED circuit were computed using a sandwich estimator of the variance which takes into account the within-patient correlation between observations [29]. Fisher's exact test was used for the two sample comparisons of the non-repeated categorical data. All statistical tests were two-tailed. A P-value <0.05 was regarded as statistically significant. All analyses were made using GenStat release 8.0 (VSN International Ltd, Waterhouse Street, Hemel Hempstead, UK) and Stata Statistical Software package, Release 9.0. (Stata Corporation 2005, College Station, TX, USA).

Results

Patient characteristics and follow-up

The clinical and demographic profiles of the patients undergoing SLED with prostacyclin are reported in Table 1. ARF was oliguric in all of them, but one, and the APACHE II score at ICU admission averaged 24; at SLED start, 27.4. Six patients had a history of recent bleeding (<48 h before the start of treatment); in four cases, the degree of bleeding was considered clinically important. The bleeding occurred as a post-operative complication (in most cases major vascular or heart surgery) in three subjects. Over 80% of the patients were on mechanical ventilation, and in many cases, hypotension and/or haemodynamic instability was already present at RRT start. Previous RRT in the form of conventional intermittent haemodialysis had been attempted in 20/35 patients (57.1%). Twenty-seven patients (77.1%) received enoxaparin as thromboprophylaxis (median daily dose 2000 UI). Out of 35 patients, nineteen survived to be discharged from the hospital, for an overall in-hospital mortality of 46%; mortality predicted by the APACHE II model at ICU admission was 42%; at RRT start, 51%.

The cohort of patients in whom SLED was performed with saline flushes had similar clinical characteristics to the original study cohort, their average APACHE II score being 24.5 (SD 4.0) at ICU admission and 25.8 (SD 3.6) at SLED start. Sixteen of them (55.2%, $P=0.11$ with respect to patients on prostacyclin) received enoxaparin as thromboprophylaxis (median daily dose 2000 UI). We could not identify major differences in the clinical characteristics related with the risk of bleeding, such as platelet count, aPTT and liver function tests at the start of SLED (data not shown).

Overall, 185 SLED sessions were carried out with prostacyclin. The median number of SLED sessions per patient was four (range 1–19; interquartile range 3–7). Planned duration was 8, 9 and 10 h in 125 (67.6%), 16 (8.6%) and 44 (23.2%) of the sessions, respectively. Ninety-seven sessions in 29 patients were performed with saline flushes. The median number of SLED sessions per patient was three (range 1–9; interquartile range 2–4). Planned duration was 8 h in all cases.

Safety

Out of 35 patients, two patients undergoing SLED with prostacyclin (5.7%; 95% CI: 0.7–19.2) had clinically important bleeding (two episodes of melaena corresponding to one episode per 100 person-day on SLED). No patients required urgent surgery for bleeding control, and no death could be attributed to haemorrhage. No patient with a history of recent haemorrhage as a comorbidity had new bleeding episodes. Out of the 29 patients, three, in whom SLED was performed with saline flushes had clinically important bleeding (10.3%; 95% CI: 2.2–27.3; $P=1.0$) for the comparison with prostacyclin; two were episodes of melaena and the other one was of haematochezia.

With the use of prostacyclin the platelet count did not decrease over all the days of the SLED treatments. At the beginning of SLED with prostacyclin, platelet count was on average 173 000/mm^3 (range 29 000–326 000) and at the end it was 174 000/mm^3 (range 39 000–465 000); the estimated daily change in platelet count did not statistically differ from zero, being +0.8% (95% CI: −3.3% to +5.1%; $P=0.69$). The daily change in platelet count of each of the 35 patients is reported in Figure 1, which shows that there was no appreciable difference between patients.

Therapeutic intervention for hypotension was required in 45/185 (20 patients) of the sessions (24.3%; 95% CI: 17.4–32.9).

The change in systolic blood pressure during the 15 min time period of prostacyclin infusion before connecting the patient to the circuit was on average −2.2 mmHg at 5 min, −4.8 mmHg at 10 min and −4.8 mmHg at 15 min ($P<0.001$ for the overall change).

During SLED, systolic and diastolic blood pressures decreased on average, respectively, by −4.4 mmHg (95% CI: −3.2 to −5.6; $P<0.001$) and −4.0 mmHg (95% CI: −3.2 to −4.9; $P<0.001$), with respect to

Table 1. Demographic and clinical characteristics of patients on SLED with prostacyclin

Age (years)	72.1 (11.4)
Males	25 (71.4)
APACHE II score	
ICU admission	24.1 (7.5)
SLED start	27.4 (5.1)
Serum creatinine (mg/dl)	5.0 (1.8)
BUN (mg/dl)	94.7 (42.7)
Oliguria	34 (97.1)
Intermittent haemodialysis before starting SLED	20 (57.1)
Mechanical ventilation	28 (80)
Post-operative status	18 (51.4)
Recent major vascular or heart surgery	15 (42.9)
Systolic blood pressure	112.3 (21.7)
Diastolic blood pressure	56.6 (13.1)
Heart rate	87.4 (15.9)
Use of vasopressors	22 (62.9)
Sepsis	17 (48.6)
Platelet count $<100\,000/mm^3$	8 (22.9)
Prothrombin activity <50%	14 (28.0)
Prophylaxis with low-molecular-weight heparin	27 (77.1)

Variables are reported as mean (SD) or number (%).

baseline values (remaining, however, unchanged if compared with the values during the test infusion; data not shown); heart rate increased by +2.1 bpm (95% CI: 1.1–3.1; $P = 0.001$). The hourly change of each of these parameters is reported in Figures 2–4, respectively. It is worth noting that, following an initial drop, blood pressure tended to increase over the course of the treatment eventually reaching values that were close to the baseline levels.

In patients requiring vasopressor administration, the drop in systolic and diastolic blood pressure during SLED was not statistically different from those not requiring vasopressor administration, though the heart rate increased less ($P = 0.012$). In the only patient with pre-dialysis systolic blood pressure persistently below 80 mmHg (a patient suffering from cardiogenic shock, who underwent 10 SLED sessions and whose pre-dialysis systolic blood pressure was 71.5 mmHg on average), systolic and diastolic blood pressures and heart rate during SLED did not change significantly [change from baseline: −1.4 (SE 1.5), +0.2 (SE 1.0) and +1.9 (SE 1.6), respectively; $P > 0.05$ for all] and only 3 of the 10 sessions required therapeutic interventions for hypotension.

In 2 sessions out of 185, SLED had to be interrupted for refractory hypotension; in two further cases the interruption was due to ventricular arrhythmias.

Efficacy

Out of the 185 daily sessions performed, only 19 (in 11 patients) were prematurely interrupted (10.3%; 95% CI: 5.4–18.6) after an average 58.5% of the prescribed treatment time; in nine sessions (seven patients) out of 185 (4.9%), SLED was discontinued for circuit clotting, in four for CVC malfunctioning

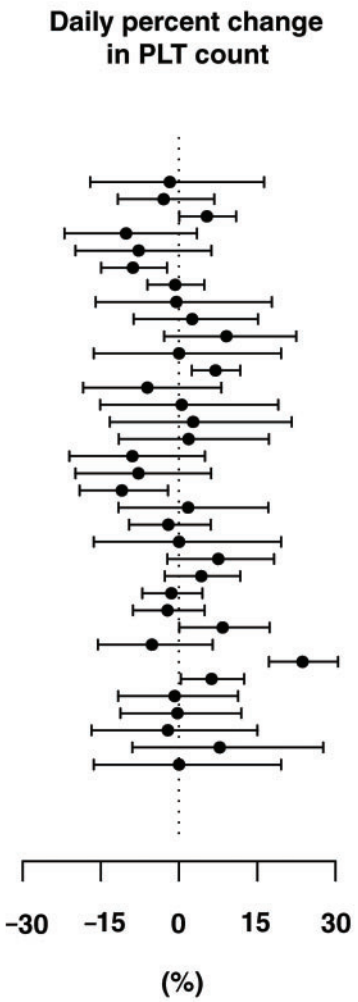

Fig. 1. Daily change in platelet count in each of the 35 patients (solid circles); bars represent 95% CIs. The vertical line represents the null value, i.e. zero change in platelet count. Patients whose bars cross the vertical line had no statistically significant change in platelet count. PLT, platelet.

(two patients), in four for haemodynamic instability (hypotension two sessions, ventricular arrhythmias two patients), in one for elevated transmembrane pressure and in one for impending death. In the patients treated with prostacyclin, we found no significant difference by LMWH administration in the rate of premature interruptions [9.9% (16/161 sessions) with and 12.5% (3/24) without LMWH; $P = 0.71$], the platelet count, the aPTT and liver function tests at the start of SLED (data not shown). Blood restitution was accomplished in the vast majority of the patients on SLED with prostacyclin; in fact, it was complete in 166 sessions (90%) and partial in 6 (3%); total loss of circuit blood complicated 13 sessions (7%).

There was a substantial difference in the rate of premature interruption between the cohort of patients in whom SLED was performed with prostacyclin and the cohort of patients in whom SLED was performed with hourly saline flushes only. In fact, in the latter cohort, 39 out of 97 sessions performed in 22 patients

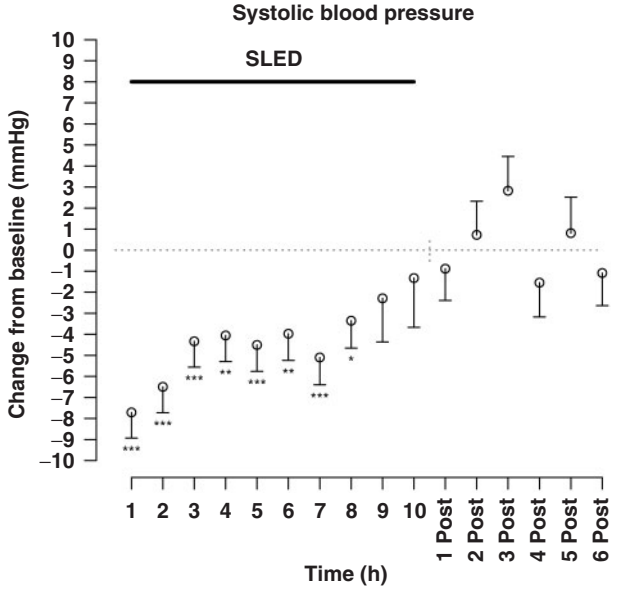

Fig. 2. Hourly change from baseline during SLED and the following 6 h in systolic blood pressure. Baseline is computed as the average of the six hourly measurements preceding the start of each SLED session. Bars refer to standard error; symbols refer to *P*-values as follows: $*P < 0.05$ but >0.01; $**P < 0.01$ but >0.001; $***P < 0.001$.

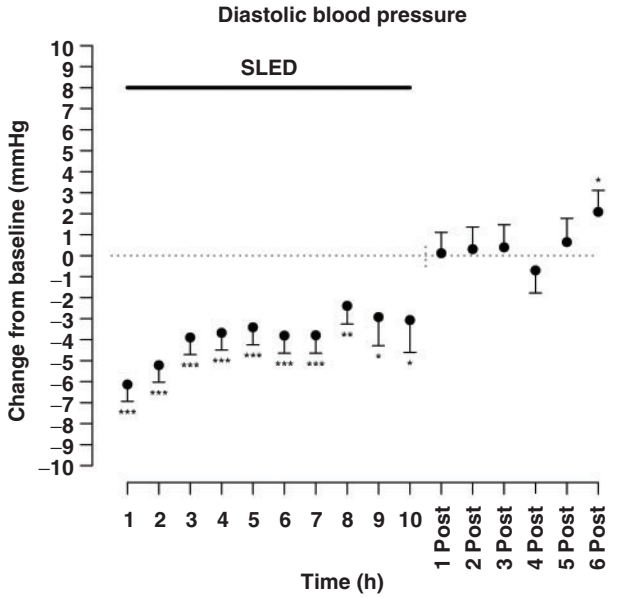

Fig. 3. Hourly change from baseline during SLED and the following 6 h in diastolic blood pressure. Baseline is computed as the average of the six hourly measurements preceding the start of each SLED session. Bars refer to standard error; symbols refer to *P*-values as follows: $*P < 0.05$ but >0.01; $*P < 0.01$ but >0.001; $***P < 0.001$.

were prematurely interrupted (40.2%; 95% CI: 27.8–54.0; $P < 0.001$ for the comparison with prostacyclin use). This higher rate of premature interruptions was not significantly influenced by LMWH administration for thromboprophylaxis: in fact, the incidence of premature interruptions was 9.9% (16/161 sessions) with LMWH/prostacyclin *vs* 35.6% (21/59 sessions) with LMWH/saline flushes ($P = 0.007$), and it was 12.5% (3/24 sessions) with no-LMWH/prostacyclin *vs* 47.4% (18/38) with no-LMWH/saline flushes ($P = 0.005$).

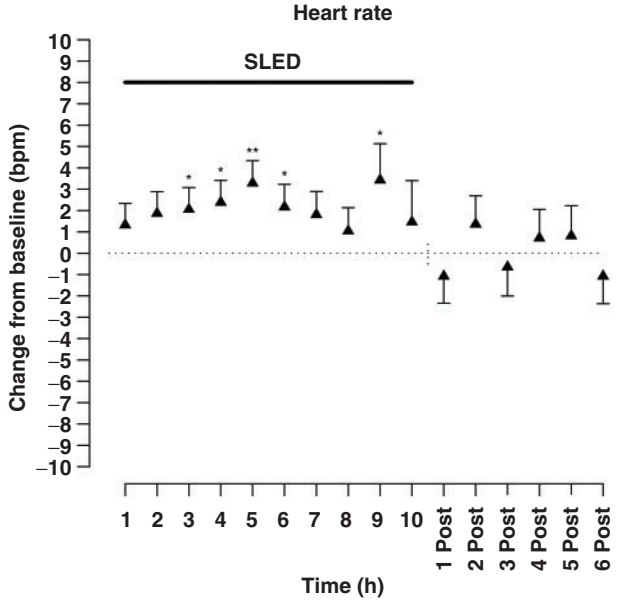

Fig. 4. Hourly change from baseline during SLED and the following 6 h in heart rate. Baseline is computed as the average of the six hourly measurements preceding the start of each SLED session; bpm, beats per minute. Bars refer to standard errors; symbols refer to *P*-values as follows: $*P < 0.05$ but >0.01; $**P < 0.01$ but >0.001; $***P < 0.001$.

The average dialysis urea clearance of 78.9 ml/min did not drop significantly at the end of the sessions, being 78.0 ml/min on average. Average urea reduction ratio at the first SLED session was 0.50 (SD 0.12). Forty-six SLED sessions were performed without weight loss; in the remaining, the prescribed and obtained net ultrafiltrations (i.e. weight loss per treatment) were, respectively, 1.961 (range 0.5–5) and 1.991 (range 0.5–5.0), while total ultrafiltration per session was 2.981 (range 1.06–6.14).

Discussion

Our study highlights several important points about the use of prostacyclin in critically ill patients with ARF treated with SLED. First of all, a dose of 6 ng/kg/min (i.e. 50% higher than that used in a previous study at our institution on CRRT patients) [16] has an excellent efficacy as antihaemostatic agent for SLED, demonstrated by the low rate (only 5%) of sessions interrupted because of circuit clotting, as compared with SLED performed with saline flushes only. In fact, about 90% of SLED sessions with prostacyclin were completed as prescribed, and even in those prematurely interrupted, about 60% of the prescribed treatment was accomplished, allowing the delivery of an adequate RRT dose.

Secondly, prostacyclin use did not appear to increase the risk of bleeding. Thirdly, in spite of its known vasodilatory effect, prostacyclin use appeared reasonably safe, even for patients with haemodynamic instability.

Several limitations of our study are to be taken into account. First, as a prospective cohort of control patients was lacking, we could not fully evaluate the effect of prostacyclin by direct comparison with SLED performed without antihaemostatic agents. However, the difference in the rate of circuit clotting with prostacyclin as compared with that with saline flushes both in our own retrospective series and in previous reports [1–3,5] is so large that it can hardly be explained by other confounding factors. Secondly, as the present study was a single-centred one, the results might not hold true in other clinical settings. In this regard, however, it is to be underlined that the clinical practice of RRT and of SLED at our ICU resembles that of most centres involved in the care of critically ill patients with ARF [1,2,4,5,20,26].

On the other hand, several issues of this study are noteworthy. Objective criteria for treatment interruption were established a priori. Data were prospectively recorded, thus providing the exact time and reason of failure, as well as the detailed description of the haemodynamic profile. Even after taking into account the use of thromboprophylaxis with LMWH, our findings did not change substantially. Finally, our study population is likely to be a representative sample of ICU patients with ARF who are candidates for RRT, in particular for the longer lasting forms of daily RRT.

In our series, <6% of the patients had clinically important bleeding, under the form of upper gastrointestinal bleeding. It is well known that use of antihaemostatic drugs during RRT in patients with ARF could further complicate the high haemorrhagic risk linked to the uraemic syndrome itself, as well as to the frequent presence of predisposing conditions such as recent surgery, disseminated intravascular coagulation, hepatic failure, etc. [23]. Thus, it is not surprising that the reported incidence of bleeding episodes during RRT in ARF patients ranges from 6% to 30–50% [30–35], causing death in up to 9–15% of them [30,31]. Data about haemorrhagic complications in the course of SLED are scanty: in one series, no episodes of haemorrhage related to heparin anticoagulation were reported for 56 sessions in 24 patients [3], while in one other series, two patients out of 37 (5.4%) had bleeding episodes during SLED [2]. In our study, the use of prostacyclin was associated with similar haemorrhagic risk, which was in any case lower than that (17.4%) previously documented in a prospective cohort study of ARF patients on RRT at our institution [21]. Our study thus confirms previous reports about safety of prostacyclin use as to the haemorrhagic risk in patients with ARF [16]: the incidence rate of clinically important bleeding, in fact, was as low as 1.1 episode per 100 days of SLED. Moreover, at variance with what has been reported for other antihaemostatic drugs [30,31], we observed no relevant variation in platelet count values during RRT with prostacyclin.

Due to its vasodilatory properties, prostacyclin decreased both systolic and diastolic arterial blood pressures. However, the blood pressure decrease was apparently well tolerated by the patients. In fact, therapeutic interventions for hypotension were needed in less than a quarter of the sessions and, most importantly, <1% of the SLED sessions had to be interrupted due to refractory hypotension. During conventional intermittent RRT, an incidence rate as high as 61% of hypotension requiring therapeutic intervention has been recently reported [36], whilst few data are currently available about the incidence of hypotension in other forms of RRT, especially during CRRT modalities. In the case of SLED, values from ~14% [2,5] to 25% [4] of patients and up to 359 episodes of hypotension in 367 sessions [1] have been recently reported; thus, the risk of 24.3% in our patients configures a favourable safety profile in the clinical context we have studied.

SLED was prematurely interrupted in only 10% of the cases, due to circuit clotting in only half of them. Literature data clearly indicate that, as in the case of other RRT modalities, clotting of the extracorporeal circuit still represents a major limitation also in the course of SLED [37]. Unfractionated heparin is the most commonly utilized antihaemostatic drug for this hybrid RRT modality with different dosage schedules being used, the most common being a 1000–2000 UI loading dose followed by the infusion of 500–1000 UI/h [5,6]. With this regimen, even though no extracorporeal circuit clotting has been reported in one study [4], other series reported clotting that required circuit replacement in 17–26% of treatments [1,2,5]. Moreover, clotting rates in the course of SLED can range from 29% to 46% if no antihaemostatic agent is used [1,3,5].

Circuit clotting still represents the Achille's heel of RRT, since it impairs the filter efficiency, reduces the treatment adequacy due to hours off treatment, increases the engagement of nursing time for frequent circuit changes and causes blood loss due to partial or null restitution of the blood contained in the extracorporeal circuit thus augmenting the transfusional needs [5,6,10]. Several methods alternative to heparin have been used for RRT over the last 30 years [37], but no consensus currently exists on which anticoagulant should be the first choice for patients on RRT [10]. However, the most recent guidelines for RRT in ARF patients do recognize that the majority of ICU patients with ARF require some form of anticoagulation for successful RRT, and that anticoagulation is one of the most important components of RRT [10]. In our patients, the incidence of circuit clotting with the use of prostacyclin was ~5% of the sessions, a figure which compares favourably with the rates previously documented in the literature; moreover, as a complete or partial restitution of the circuit blood was possible in ~93% of cases, blood losses due to RRT were reasonably low.

The efficacy of the prostacyclin-based treatment can be summarized as follows: about 9 out of 10 SLED sessions with prostacyclin were completed in the prescribed time; in the remaining sessions, the ratio of delivered to prescribed dose, based on time of treatment, was 60%; the prescribed net ultrafiltration was virtually always achieved. Thus, the efficacy of this RRT modality was excellent and in line with the results reported in the literature for similar treatments [1,2,4,5] and for CRRTs [4]. A drawback of prostacyclin use remains the high cost (one drug vial per SLED, at 107 euros/treatment in Italy) as compared with some other antihaemostatic strategies.

In conclusion, the use of prostacyclin as an antihaemostatic drug for SLED is safe and efficacious in patients with ARF on RRT. Even though the ideal regimen to prevent clotting in the extracorporeal circulation during SLED remains to be found, the use of prostacyclin represents an easy and physiological method to maintain extracorporeal circuit patency. Further studies are needed to directly compare this method with other antihaemostatic strategies, in order to define its exact role for SLED.

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