https://doi.org/10.31925/farmacia.2021.1.10 **ORIGINAL ARTICLE**

HEPARIN PROVIDES LONG TIME SURVIVAL FOR CIRCUITS IN THE NEONATAL AND INFANT CONTINUOUS RENAL REPLACEMENT THERAPY

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Abstract

The neonatal and infant continuous renal replacement therapy (CRRT) allows proper nutrition and medication and avoids complications such as fluid overload and hydro-electrolytic imbalances. One of the major factors on which CRRT success depends is anticoagulation. There are several options for anticoagulation and one of the first used is systemically administered heparin. We conducted a retrospective, observational, descriptive study between January 2015 and August 2020 among patients with hemodiafiltration admitted in the Neonatal Intensive Care Unit (NICU) – "M. S. Curie" Children's Hospital, Bucharest, Romania. A group of 25 patients of CRRT-CVVHDF (continuous venous-venous hemodiafiltration) were analysed, for which the duration of administration was longer than 6 hours. We evaluated the life of the circuit, the total duration of CRRT, coagulation, haemoglobin values, platelets count, the need for substitution therapy and the adverse effects of heparin. Recently there are studies that recommend other ways of anticoagulation in neonatal CRRT as a first intention, but the successful use of heparin is still motivated due to the very long lifespan of the circuit compared to previous studies, without major complications related to anticoagulation.

Rezumat

Terapia de substituție renală continuă neonatală și infantilă (*CRRT - continuous renal replacement therapy*) permite nutriția și medicația adecvate și evită complicații precum supraîncărcarea lichidelor și dezechilibrele hidro-electrolitice. Unul dintre factorii majori de care depinde succesul CRRT este anticoagularea. Există mai multe opțiuni pentru anticoagulare și una dintre primele utilizate este heparina administrată sistemic. S-a efectuat un studiu retrospectiv, observațional și descriptiv în perioada ianuarie 2015 - august 2020 în rândul pacienților cu hemodiafiltrare în Secția Terapie Intensivă Nou Născuți a Spitalului Clinic de Urgență pentru Copii „M. S. Curie", București, România. Au fost analizați 25 de pacienți de CRRT-CVVHDF (hemodiafiltrare veno-venoasă continuă) a căror durată de administrare a fost mai mare de 6 ore. S-a analizat durata de viață a circuitului, durata totală a CRRT, coagularea, valorile hemoglobinei, numărul de trombocite, necesitatea terapiei de substituție și efectele adverse ale heparinei. Recent s-au publicat studii care recomandă alte modalități de anti-coagulare în CRRT neonatală ca primă intenție, dar folosirea heparinei încă se dovedește a fi un succes, deoarece se realizează o durată de viață foarte lungă a circuitului în comparație cu studiile anterioare, fără complicații majore legate de anticoagulare.

Keywords: neonatal CRRT, heparin, circuit lifespan

Introduction

Continuous renal replacement therapy has an important role in treating the critically ill patient, allowing for adequate nutrition and medication and avoiding some specific complications such as fluid overload and hydro-electrolytic imbalances. Lately, CRRT has started to be used more frequently in neonates and young children. One of the major factors on which CRRT success depends is anticoagulation. Contact of the blood with the extracorporeal circuit activates platelets, as well as inflammatory and procoagulant factors. In the paediatric population, these phenomena are exacerbated due to the slowed and turbulent blood flow, the small catheter and the physiologically increased haematocrit. The clots in the extracorporeal circuit can be small, reducing the clearance of the solutions or major, leading to the compromise of the filter and implicitly compromise of the circuit [27, 28]. Compromising the circuit and restoring a new circuit decreases the efficiency of the therapy, while increasing the costs and the risk of side effects by exposure to new blood products. In both adults and children, many

ways have been tried to slow down the formation of clots in the circuit through technical changes (adequate flow, adequate position, decreased haematocrit in the filter, prompt reaction to alarms) but also by applying various methods of anticoagulation [15]. The most commonly used options for CRRT anticoagulation include systemic heparin and regional citrate [28]. Prostacyclin, low-molecular-weight heparin, thrombin antagonists (argatroban and bivalirudin), heparin with protamine reversal, heparinoids, and platelet-inhibiting agents are less common options [1, 6, 10, 21-23]. Systemically administered heparin was one of the first methods used and is still used with very good results.

Materials and Methods

It was conducted a retrospective study between January 2015 and August 2020 on patients with hemodiafiltration in the NICU - "M. S. Curie" Children's Hospital, Bucharest, Romania. A group of 25 patients of CRRT-CVVHDF (continuous venous - venous hemodiafiltration) were analysed, whose duration of administration was longer than 6 hours. In all cases an informed consent was obtained from the patients' legal guardians [24].

All statistical analyses were performed using a statistical analysis software SPSS 15.3 and Excel and the results are presented as mean ± standard deviation and percentages.

For this therapy it was used the Prismaflex machine, Set HF 20, membrane AN 69 ST. 65% of patients were neonates and the rest were small infants. The maximum age of the patients enrolled was 9 months. Patient weight at the beginning of therapy was between 2200 g and 9000 g (average of 3738 g). The survival rate was 20% (5/25) (Figure 1).

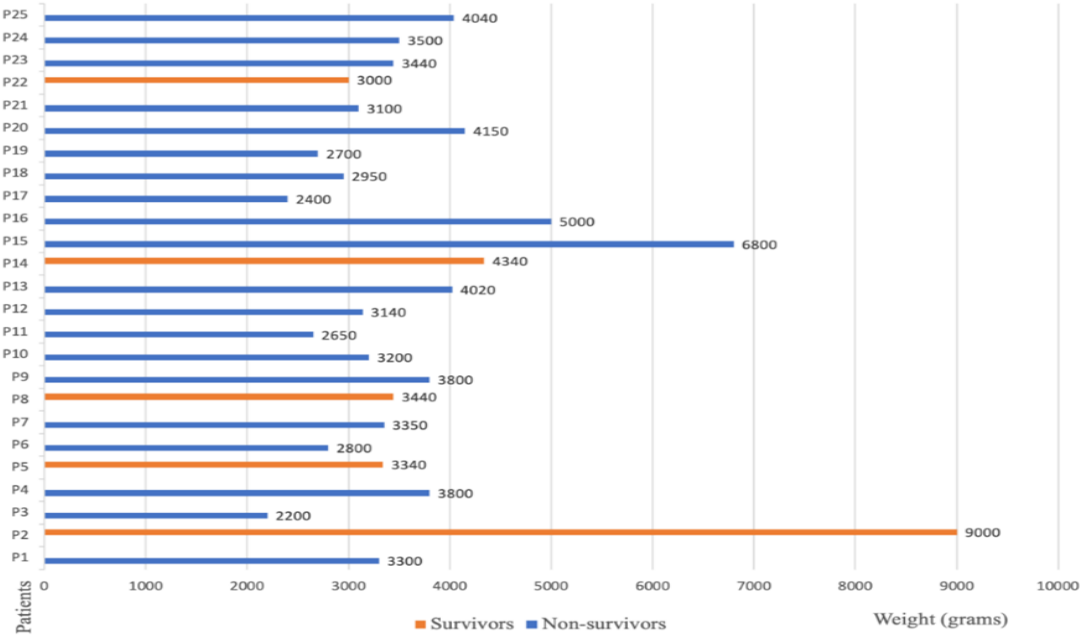

Figure 1.
Patients weight distribution at the beginning of CRRT

Patients had the following diagnoses: congenital heart disease - mainly after cardiac surgery, sepsis, perinatal asphyxia, renal malformations and renal vessel thrombosis, bullous epidermolysis (Figure 2).

For all patients, the anticoagulation therapy was accomplished using systemic heparin administered in the pre-filter circuit. Initially, a bolus of 20 - 40 IU/kg was administered during cannulation and then in continuous infusion 5 - 10 - 20 IU/kg/h [7]. For bleeding monitoring it was used ACT (activated clotting time) and/or APTT (activated partial thromboplastin time). The target of ACT was 180-220s and for APTT twice the normal value (60-80s) [9, 17, 18]. We analysed the lifetime of the circuit, the total duration of CRRT, coagulation, haemoglobin values, platelets count, the need for substitution therapy and the adverse effects of heparin.

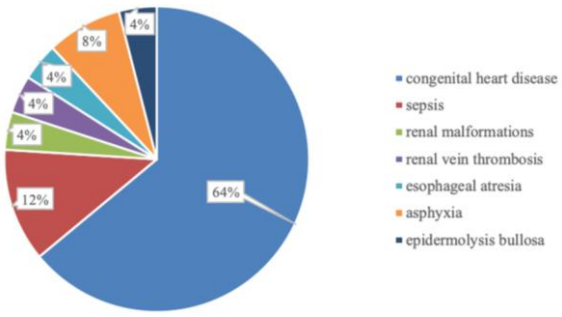

Figure 2.
Primary diagnosis of the patients undergoing CRRT

Results and Discussion

Heparin were discovered in 1916 by MacLean, but used since 1960 for many indications [2, 19]. It has a lifespan of 30 minutes in healthy patients and 90 minutes in patients with acute kidney injury (AKI). Heparin couples with antithrombin III and thrombin and forms a tertiary complex that inactivates factors IX, X, XI and XII. Antithrombin III binds to thrombin and blocks its effect of converting fibrinogen to fibrin. Heparin also inhibits the enzymes from leukocytes, reduces free radical generation, improves the activity of phagocytes and monocytes that eliminate fibrin micro-aggregates and prevents thrombin-induced vaso-spasm [14, 19]. Routinely, the effect of heparin is monitored by APTT and ACT. APTT measures the therapeutic inactivation of factors Xa, IX and thrombin. Unfortunately, this laboratory test is not very accurate in monitoring heparin dosing. There are certain clinics that recommend the assay of the Xa anti-factor to monitor the therapeutic level of heparin, but this investigation is not of routine in current practice [25]. Usually, children have lower levels of antithrombin III, especially in sepsis. It is necessary to monitor the serum level of antithrombin III, and if the level is less than 70%, it is required to be additionally administered [9]. In Romania, this is not a routine practice. ACT has the advantage of being bedside-available and uses whole blood, but the results can be influenced by haemoglobin, platelet count, fibrinogen, bilirubin, triglycerides level and blood temperature [1, 21]. Therefore, it seems that the APTT value is in a closer correlation than ACT for heparin monitoring. For a better approach, both tests are used, after correcting the levels of fibrinogen and platelet count [16, 18, 20]. In our patients, the therapeutic approach was as follows: in 5 cases only APTT, in 1 case only ACT and in 19 cases both APTT and ACT. ACT is an easy investigation to perform and offers a fast result, therefore it was used several times per day, under the control of APTT at the central laboratory. The target for APTT was 60 - 80s, as recommended in literature [9, 17, 18, 21, 23] and in our patients the average was 76.06 s (Figure 3). The target for ACT was 180 - 220s [9, 17, 18, 21, 23]. The average in our group was 224.5 s (Figure 4).

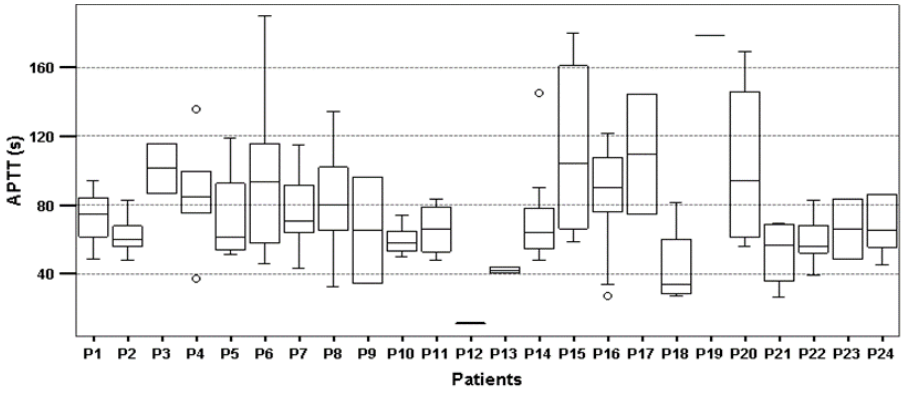

Figure 3.
Average APTT values

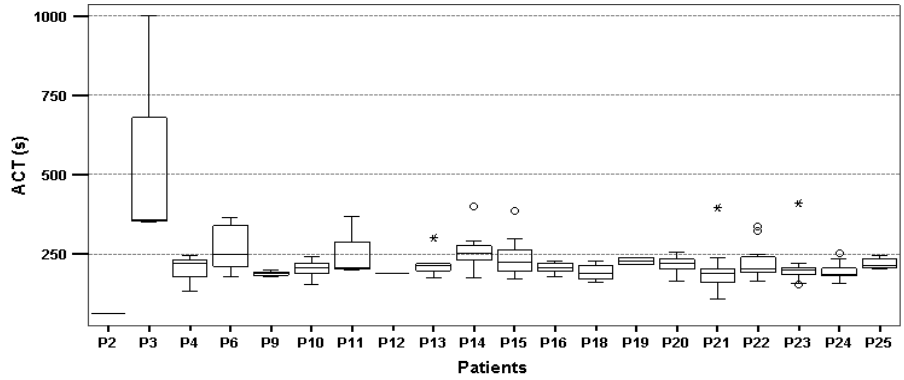

Figure 4.
Average ACT values

For ACT lower than 180 s, we administered heparin bolus 10 - 20 IU/kg/h followed by increasing the heparin rate by 1 IU/kg/h. For ACT values higher than 250 s, the heparin rate decreased until stopping the administration and/or the antidote protamine has been administered [7, 19]. Protamine sulphate is

administered very slowly because it can cause vasoplegia and hypotension and may also present side effects: allergy, pulmonary hypertension, bradycardia, proinflammatory response activating the classic complement pathway [3, 19]. Protamine was administered in 3 cases, with immediately good results: no bleedings, drop of the ACT and APTT values and no hypotension.

The average CRRT time was 205.8 hours, as depicted in Figure 5. A report of the Prospective Paediatric Continuous Renal Replacement Therapy Registry shows that most children received CRRT between 24 - 168 hours [20].The longest time for a survivor, in our group was 336 hours (Figure 5). The average lifespan of a circuit was 78.9 hours compared to the 72 hours recommended by the manufacturer. However, studies show, in neonates, using similar machines and techniques, a much shorter lifespan. The average life of the filter in these studies was 31 - 51.1 hours [5, 11, 26]. In our study, the longest time CRRT without any changes is 240 hours (Figure 5).

The mean platelet count was 99.8 * 10^3/μL and platelet concentrate was administered to maintain a value of above 100 * 10^3/μL [9]. All patients required platelet concentrate administration (Figure 6). The decrease in platelet count was observed in all patients after the first 72 hours of CRRT, similar with other studies [13].

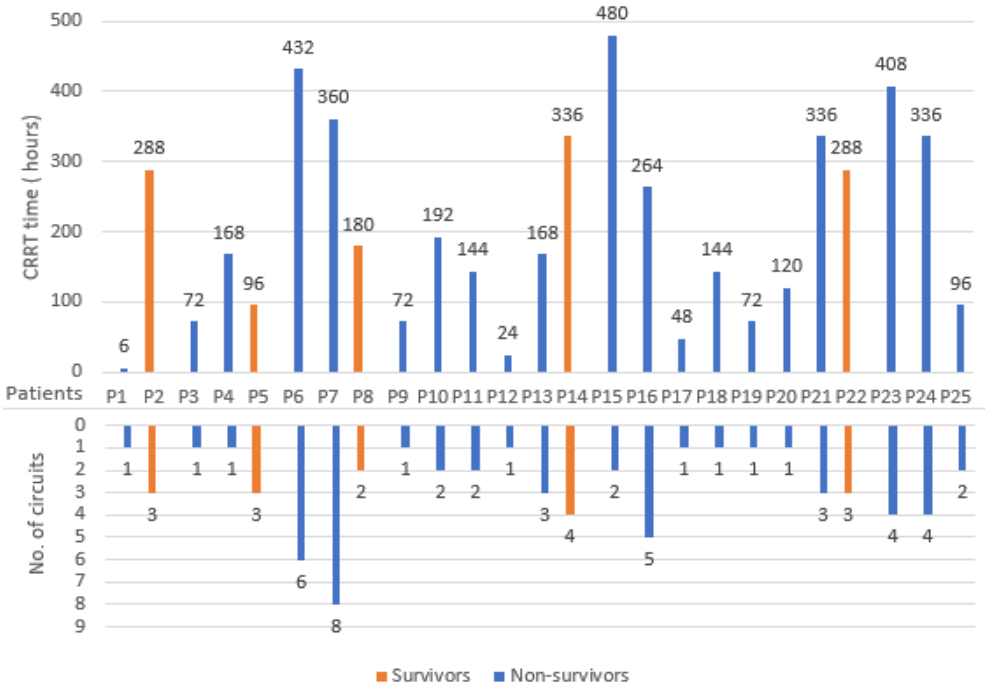

Figure 5.
The circuits lifespan

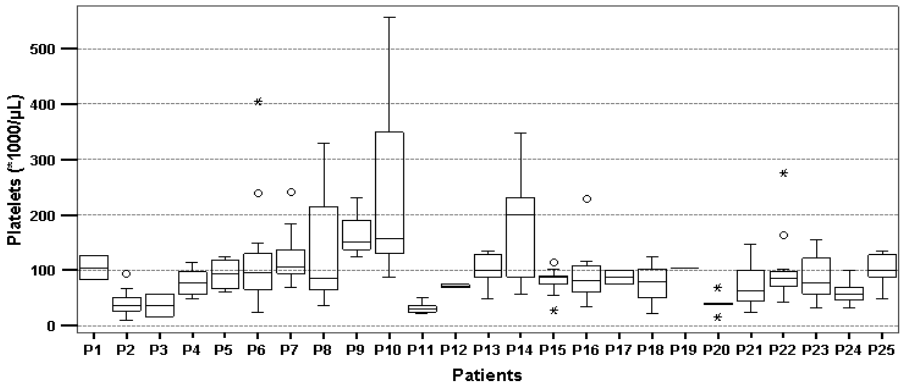

Figure 6.
Average platelet count

This phenomenon can have several explanations: association with cardiopulmonary bypass, sepsis, immune-mediated thrombocytopenia due to contact with the filter membrane, sepsis, medication received [12], thromboembolism and HIT (heparin induced thrombocytopenia) [13, 14]. The average of haemoglobin

over CRRT was 11.52 g/dL with administration of erythrocyte concentrate in all cases (Figure 7).
The mean value of fibrinogen was 149.9 mg/dL (Figure 8) and was corrected with fresh frozen plasma (FFP) and cryoprecipitate, although the use of fresh frozen plasma may shorten the life of the filter [8].
In one of the cases, the prothrombin mutation, probable the presence of C677T mutation and A1298C mutation created a procoagulant status and the circuit clogged faster than usually (lifespan of the circuit was of 24 hours).

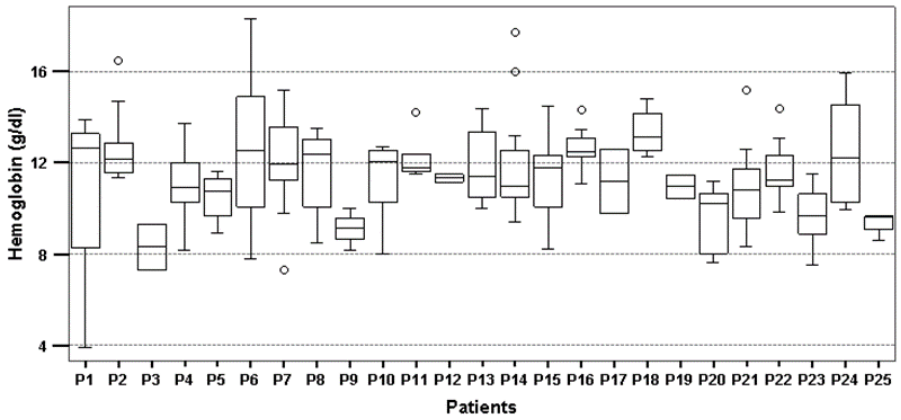

Figure 7.
Average haemoglobin values

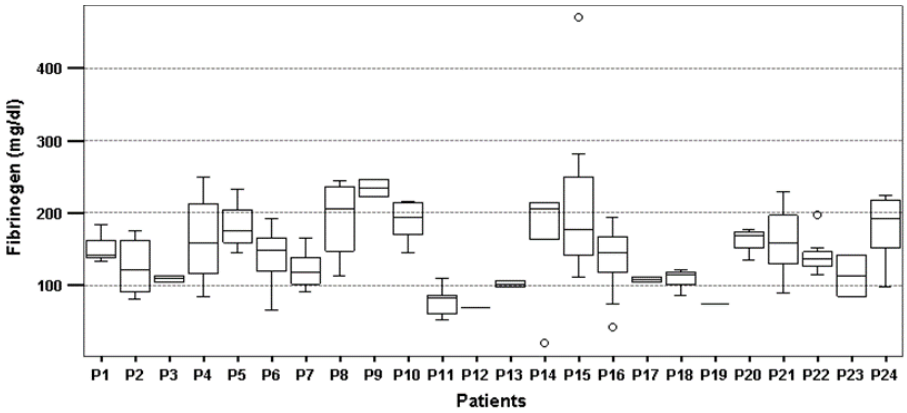

Figure 8.
Average fibrinogen values

Heparin may increase transaminases values, which have been reported in over 80% of the patients receiving heparin. The mechanism for this effect has not been identified but is reversible [19]. However, in CRRT, we cannot attribute this effect only to heparin. The elevated liver enzymes can also be attributed to sepsis, liver failure in the context of heart failure, hepatotoxic medication, or parenteral nutrition. In our study, the incidence of increased transaminases was 44%, without being able to establish a correlation with CRRT. Because the heparin molecule is not eliminated by CRRT, heparin administration has an additional risk of bleeding [17, 19], occurring in 10 - 15% of the patients. Anticoagulation has been attempted with continuous infusion of heparin pre-filter and continuous infusion of protamine post filter, but it has been found this does not increase the life of the circuit and may even cause a rebound of heparin and furthermore, the systemic anticoagulative effects of protamine and heparin could be summed [21]. In the case of our patients, bleeding occurred in 72% of patients and had the following locations: bleeding at the cannula site (3/25), endotracheal (4/25), oral (5/25), pulmonary (4/25), digestive (3/25), skin (2/25), urethral (1/25), hemopericardium (1/25) and at the drains (2/25). No massive cerebral haemorrhage was reported, and not a single haemorrhagic event was causative of death. Heparin resistance may also occur during administration of heparin - the mechanism of production is by alteration or deficiency of anti-thrombin III. [17]. Rarely, heparin-induced allergy and heparin-induced aldosterone suppression have been reported, either asymptomatically or with hyper-kalaemia in 5 - 10% of patients [19]. No patient has been reported in our study with such complications. For patients with Multiple Systems Organ Failure who need CRRT, heparin should be avoided and regional citrate is indicated. This method requires less careful

monitoring than in the case of heparin administration, because, compared to heparin citrate administration, it has a lower risk of bleeding [27], but presents a higher frequency of systemic hypocalcaemia. In coagulopathies or liver failure, neither heparin nor citrate is recommended and then other options such as prostacyclin are considered, still with limited use in the paediatric population [17]. Prostacyclin also has a heparin-sparing effect, by inhibiting platelet factor 4 by 85 - 95%, which consequently inhibits heparin. It can be used when heparin doses are escalated and, in order to keep the desired ACT values, the dose of heparin could be decreased by association with prostacyclin. It appears to extend the life of heparin by 40%. It can be used alone, or at the same time with heparin, by pre-filtering [10]

Conclusions

Pre-filter administered heparin into the anticoagulant system is a safe and effective method of anti-coagulation in CRRT in new-borns and small infants. The advantages of heparin are: reduced costs, presents an immediate antidote and the medical staff is familiar with its administration and follow-up. The major disadvantage is the systemic anticoagulation and the risk of bleeding with multiple blood products transfusions. We still successfully use the "old" heparin due to the very long lifespan of circuits compared to previous studies, without major complications related to anticoagulation. In order to keep at least the same lifespan of the circuit with less transfusions, maybe combining a lower dose of heparin with other drugs, i.e. prostacyclin could be a further performed approach.

Conflict of interest

The authors declare no conflict of interest.

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