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Incidence of Bleeding and Filter Clotting among Children on CRRT

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Abstract

Continuous renal replacement therapy (CRRT) is a renal replacement intervention in critically-ill patients. Premature (non-elective) termination of CRRT is usually due to clotting in the extracorporeal circuit, most commonly the filter. To detect incidence of bleeding and thrombotic complications during CRRT. The study were conducted on 58 children on CRRT, all were subjected to full history taking, examination, basic laboratory data, CRRT prescription parameters and changes, duration of sessions, vascular access data, anticoagulation type, dose, adjustment, laboratory monitoring tests values (aPTT, Antithrombin III), bleeding or extracorporeal circuit clotting were all recorded. Among 58 studied sessions, 25 (43.1%) ended with filter clotting. The rest (33 cases representing 56.9%) were not terminated with filter clotting, in 16 (27.6%) of them the indication was cured, 8 cases (13.8%) ended with patients' death, 9 (15.5%) ended with life threatening bleeding. Bleeding incidence was 32.8% among the studied 58 cases, but was not severe in 19%, filter clotting incidence was 43.1% among studied group.

Keywords: CRRT, filter clotting, bleeding complications.

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1. Introduction

Premature (non-elective) termination of CRRT is usually due to clotting in the extracorporeal circuit, most commonly the filter. The major cause of short-lived circuits is inadequate anticoagulation [1]. Other than anticoagulation, vascular access, circuit or patient's condition (e.g. hemodynamics and prothrombotic states) [7]. Anticoagulation is generally required to maintain circuit patency [2]. Appropriate anticoagulation is a subtle balance between clotting and bleeding. Agents used include unfractionated heparin and regional citrate anticoagulation (RCA) [2]. Unfractionated heparin is the most common anticoagulant used worldwide. It inhibits factors IIa and Xa by potentiating antithrombin III. The anticoagulant effect is monitored by measuring activated plasma prothrombin time (APTT) [2]. Regional citrate anticoagulation depends on administration of citrate through the extracorporeal circuit to bind calcium and prevent clotting, together with a concomitant calcium infusion to the patient [1].

1.1 Aim of work

To predict incidence of bleeding as well as thrombotic complications in children on CRRT.

2. Study methods

In this cross sectional study, fifty eight children were included, admitted in intensive care units in Cairo University Pediatrics Hospital, aged up to 13 years old, required CRRT due to either development of AKI in association with acute critical illness, AKI complicating an acute renal disease, acute need for renal replacement in a critically ill child with known/ prior CKD or non-renal indications as poisoning and metabolic disorders. All patients were subjected to full history taking and examination including age, vital data (heart rate, blood pressure, respiratory rate), Indication for CRRT, System failures and supports, conditions associated with bleeding or thrombotic tendency. Baseline laboratory assessment including complete blood count (Hb %, hematocrite, platelet count, TLC), coagulation profile (PC, PT, APTT, and INR), and antithrombin III, pre and post heparin infusion during sessions. CRRT prescription and set up were recorded.

Anticoagulation data including type, dose, laboratory monitoring and adjustment were recorded. Circuit pressures and their trends, required changes in blood flow rate and ultrafiltration, Filter clotting, Any bleeding complication and management, Duration and reason of session termination, filter status at the end (clotted or not), and coagulation status were all recorded.

2.1 Ethical committee approval

The study was approved by the Ethical Committee at 2021.

2.2 Statistical analysis

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations and ranges when parametric and median, inter-quartile range (IQR) when data found non-parametric. Also qualitative variables were presented as number and percentages. The comparison between groups regarding qualitative data was done by using ***Chi-square test*** and/or ***Fisher exact test*** when the expected count in any cell found less than 5 [11]. The comparison between two independent groups with quantitative data and parametric distribution was done by using ***Independent t-test*** while with non-parametric distribution were done by using ***Mann-Whitney test*** [11]. Predictors of bleeding and thrombosed filter. The confidence interval was set to 95% and the margin of error accepted was set to 5%.
P-value < 0.05: Significant (S)

3. Results and Discussion

Among the studied 58 cases, 25 (43.1%) complicated with filter clotting, 17(29.3%) of the clotted filters ended successfully and the indication of CRRT was cured, while the rest (8, 13.8%) ended without resolution of indication. The rest of 33 unclotted filters, 16 ended with patient cure, 9 ended with life threatening bleeding, 8 ended with patient death. Larger high quality studies have predominantly focused on optimal anticoagulation however CRRT is complex and filter life is also affected by vascular access, circuit and management factors [4]. Anticoagulation is generally required to maintain circuit patency and should be kept at a low dose to mitigate bleeding complications [2]. Agents used include unfractionated and low molecular weight heparin and regional citrate anticoagulation (RCA) [2]. The present study used regional citrate as anticoagulation in only one circuit, while *Kang et al* conducted a study in *2021* on 31 patients at high risk of bleeding to investigate the safety and efficacy of regional citrate anticoagulation (RCA) after continuous renal replacement therapy (CRRT), patients were divided into RCA group (n = 17) and no anticoagulation group (NA, n = 14), their study showed that RCA treatment significantly improves clinical outcome of patients at high risk of bleeding after CRRT, safely and effectively prolongs the filter life and avoids coagulation incidences. *Raymakers-Janssen et al* also conducted a study in *2017* on children who underwent CRRT with the smallest filter in PICU between November 2011 and November 2016. Both heparin and citrate were applied according to a strict protocol. Their primary outcome was circuit survival time. Median circuit survival time with heparin was 21 h (IQR 14.5-27.5) compared to 45.2 h (IQR 37.5-52.8) with citrate ($p < 0.001$), while our result showed that median circuit survival time with heparin was 46.5 hrs., and was longer with citrate, 72hrs.this statistical significance shows that use of regional citrate significantly prolongs circuit survival time and thereby should increase CRRT efficiency when compared to heparin. This study cannot be correlated to the present study as only one circuit was anticoagulated with regional citrate anticoagulation. This present study showed no significant difference in outcome of sessions in terms of bleeding or filter thrombotic complications among different methods used for anticoagulation., (P-value= 0.908, 0.817 respectively), that goes with studies conducted by *Zhang et al., 2021* where a clinical guideline recommends continuous renal replacement therapy (CRRT) proceed without anticoagulation in patients with contraindication to citrate and increased bleeding risk. Nevertheless, the efficacy of anticoagulation-free CRRT remains inconsistent. The purpose of that systematic review was to evaluate the efficacy and safety of anticoagulant-free CRRT. The primary outcomes were filter lifespan and risk factors for filter failure.

There was no significant difference in filter lifespan and the anticoagulation-free and systemic heparin group. The regional citrate anticoagulation (RCA) protocol seems to be superior ($p <0.001$) to the anticoagulation-free protocol in terms of filter lifespan, $p = 0.53$), the conventional coagulation parameters showed poor predictive performance for filter failure and the necessity of anticoagulants use before CRRT. The optimal choice of anticoagulation strategy for critically ill patients with increased bleeding risk could be RCA under close monitoring. *Zhang et al.* conducted a study in *2022* to develop and validate a model for predicting sufficient filter lifespan in anticoagulation-free CRRT patients, the primary outcome was sufficient filter lifespan (≥24 h), and the development cohort included 170 patients. Sufficient filter lifespan was observed in 80 patients. Thirteen variables were independent predictors for sufficient filter lifespan by logistic regression, one of them was activated partial thromboplastin time (APTT). This comes in agreement with the present study results which showed a statistical significance between filter clotting in heparinized circuits and value of APTT at the end of session, (P-value =0.000), with the median APTT value till filter clotting event occurred was 49 seconds, and 67 seconds in sessions not complicated with filter clotting, which is also present in the study of *Matthew et al. in 2017. Nigel et al.* conducted a Prospective randomized controlled trial in *2017* to determine whether Continuous renal replacement therapy without anticoagulation was more likely to cause clotting compared with use of heparin strategies, (hazards ratio, 1.62; $p = 0.003$). Longer activated partial thromboplastin time (hazards ratio, 0.98; $p = 0.002$) and decreased platelet count (hazards ratio, 1.19; $p = 0.03$) were associated with a reduced likelihood of circuit clotting.

Table 1: Outcome at end of sessions among the studied patients

		Total no. = 58
Duration of sessions in hrs (technique survival)	Median (IQR)	48 (24 – 72)
	Range	10 – 168
	(<24 hrs)	5 (8.6%)
	(24-72) hrs	45 (77.6%)
	(>72) hrs	8 (13.8%)
Thrombosed filter	Not clotted	33 (56.9%)
	Clotted	25 (43.1%)
End result of sessions	No filter clotting, indication cured	16 (27.6%)
	Filter clotting, without resolution of indication	8 (13.8%)
	Filter clotting, indication cured	17 (29.3%)
	Life threatening bleeding	9 (15.5%)
	Death	8 (13.8%)
Mortality	Survived	50 (86.2%)
	Died	8 (13.8%)
Severity of bleeding	No	39 (67.2%)
	Mild	10 (19.0%)
	Life threatening	9 (13.8%)
Bleeding	No	39 (67.2%)
	Yes	19 (32.8%)
Pressure drop at the end mmHg	Median (IQR)	200 (100 – 250)
	Range	50 – 400
TMP at the end mmHg	Median (IQR)	150 (100 – 300)
	Range	45 – 480

It goes with the present study as longer APTT values were associated with reduced likelihood of circuit clotting and longer duration of session (median APTT value 67 seconds in non-clotted filters, 49 seconds in clotted ones, P-value =0.000), it goes with our study regarding platelets count too, as it showed a statistical significance between platelets count after 4 hours of sessions initiation and incidence of premature termination of sessions and filter clotting , P- value =0.048, median platelet count in clotted sessions 180 and 107 in non-clotted circuits. In this study, we found that there was a statistical significance between Antithrombin III levels done before circuit heparinization and heparin bolus dose given, patients who received higher dose of bolus heparin (median 35) showed lower Antithrombin III values (less than 80%), this goes with *Matthew et al.* study done in *2017*. *Raina et al.* in *2022* explores the adequacy of non-anticoagulation measures in the prevention of circuit clotting, findings shows that the most-effective CRRT catheter would be made of nonthrombogenic material, no cuffed and no tunneled with separate lumens for arterial and venous blood. Further, studies show that blood flow during the process is optimized at 200 ml/min, which can be lowered in the pediatric population due to more narrow catheters. Platelet count and hematocrit need to be closely monitored as levels above 450,000 × 10^6 /L and 0.40, respectively, increased risk of clotting. Predilution is a non-anticoagulation technique to reduce the risk of clotting by returning replacement solution to the blood before it reaches the filter. This present study results showed difference with *Raina et al.* in statistical significance regarding blood flow rate, platelet count and predilution technique, as our results showed no statistical relation between filter patency and duration of sessions and blood flow rate and predilution technique, p-values = 0.487, 0.846 respectively. It goes with our study in the significance between platelets count and clotting complications, as our result showed that the more the platelets count the more the incidence of clotting, p- value= 0.048. On the other hand, it differs from *Raina et al.* in statistical significance between type of vascular access used and early session termination and filter clotting, as our study did not show significance in site of vascular access insertion and incidence of clotting. *Kakajiwala et al.* identified factors associated with premature clotting of circuits during CRRT in children in a retrospective cohort study in *2017* of 26 children (median age 11.8 years) receiving 79 CRRT circuits (51 heparin, 22 citrate, 6 using no anticoagulation), they captured hourly pressure, flow, and fluid removal rates. Of the 79 circuits, 51 (64.6%) underwent unplanned filter change due to filter clotting (median duration 18.25 h, interquartile range [IQR] 9.25, 33.5 h), and 28 (35.4%) underwent scheduled change (median duration 66 h, IQR 61.00, 69.00 h). Patient age, catheter size and location, blood flow rate, and the percentage of pre-filter replacement fluid were not associated with premature clotting. Heparin circuits were less likely than citrate circuits to clot prematurely. Each 1-mmHg increase in the transmembrane or filter pressure was independently associated with a 1.5% higher risk of clotting, respectively. This goes with this study results regarding insignificance between patient's age, catheter location, blood flow rates and filter clotting (P-values 0.125, 0.69, 0.48 respectively), it goes with it also it in the insignificance of prefilter replacement relation with filter clotting (P-value =0.358). Tunneled semi-permanent vascular access devices were consistently associated with longer filter life in

Matthew et al. (2017), study. A significant confounder is that these devices were often larger internal diameter than temporary devices, this statistical significance doesn't match this study results as all catheters used were temporarily double lumen, and only one cuffed tunneled access was used in this present study. Optimal vascular access site ranked by association with longer filter life in the study conducted by *Matthew et al. 2017* is: tunneled semi-permanent, femoral or internal jugular, subclavian site, on the other hand, our study results shows no statistical significance between site of insertion of access and filter clotting. Regarding the relation between the clinical data of the patients (age, conscious state, presence of septic shock , illness severity score) and the bleeding and filter thrombotic complications occurred during session of CRRT, among 58 patients studied, 19 had bleeding complications, one of them septic shock, this showed a statistical significance (P-value =0.043), this study found no statistical significance between bleeding complications during sessions and patients' size (age, weight), PRISM score of illness. On the contrary to our study, a systematic review and meta-analysis was performed by searching PubMed (MEDLINE) and Ovid EMBASE libraries from inception to 29th February 2016 for all studies with a comparator or independent variable relating to CRRT circuits and reporting filter life *(Matthew et al., 2017)*, Patient factors associated with a statistically significant worsening of filter life included mechanical ventilation, elevated illness score, no statistical significance was found related to conscious level of the patient.

4. Conclusions

Bleeding incidence was 32.8% among the studied 58 cases, but was not severe in 19%, filter clotting incidence was 43.1% among studied group.

References

[1] R. Claure-Del Granado, E. Macedo, S. Soroko, Y. Kim, G.M. Chertow, J. Himmelfarb, T.A. Ikizler, E.P. Paganini, R.L. Mehta. (2014). Anticoagulation, delivered dose and outcomes in CRRT: The program to improve care in acute renal disease (PICARD). Hemodialysis International. 18(3): 641-649.

[2] R. Matthew, R. Wilson. (2017). Campbell Tait, in Handbook of Pharmacogenomics and Stratified Medicine.

[3] A. Kakajiwala, T. Jemielita, J.Z. Hughes, K. Windt, M. Denburg, S.L. Goldstein, B. Laskin. (2017). Membrane pressures predict clotting of pediatric continuous renal replacement therapy circuits. Pediatric Nephrology. 32: 1251-1261.

[4] M. Brain, E. Winson, O. Roodenburg, J. McNeil. (2017). Non anti-coagulant factors associated with filter life in continuous renal replacement therapy (CRRT): a systematic review and meta-analysis. BMC nephrology. 18(1): 1-27.

[5] R. Raina, S. Sethi, A. Khooblall, V. Kher, S. Deshpande, K. Yerigeri, A. Pandya, N. Nair, N. Datla, M. McCulloch. (2022). Non-anticoagulation pediatric continuous renal replacement therapy methods to increase circuit life. Hemodialysis International. 26(2): 147-159.

[6] P.A. Raymakers-Janssen, M. Lilien, I.A. van Kessel, E.S. Veldhoen, R.M. Wösten-van Asperen, J.P. van Gestel. (2017). Citrate versus heparin anticoagulation in continuous renal replacement therapy in small children. Pediatric Nephrology. 32: 1971-1978.

[7] C. Ronco, Z. Ricci. (2015). Pediatric continuous renal replacement: 20 years later. Intensive care medicine. 41: 985-993.

[8] A.Y. Wang, R. Bellomo. (2018). Renal replacement therapy in the ICU: intermittent hemodialysis, sustained low-efficiency dialysis or continuous renal replacement therapy? Current opinion in critical care. 24(6): 437-442.

[9] W. Zhang, M. Bai, Y. Yu, X. Chen, L. Zhao, X. Chen. (2021). In Continuous renal replacement therapy without anticoagulation in critically ill patients at high risk of bleeding: A systematic review and meta-analysis, Seminars in Dialysis. Wiley Online Library: 2021; pp 196-208.

[10] W. Zhang, M. Bai, L. Zhang, Y. Yu, Y. Li, L. Zhao, Y. Yue, Y. Li, M. Zhang, P. Fu. (2022). Development and external validation of a model for predicting sufficient filter lifespan in anticoagulation-free continuous renal replacement therapy patients. Blood Purification. 51(8): 668-678.

[11] Y H Chan. (2003). Biostatistics 104: correlation analysis. Singapore Medical Journal.