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Review paper

Practical issues of regional anticoagulation during continuous renal replacement therapy

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Abstract

Introduction: Extracorporeal blood purification techniques have become a well-established part of routine practice in intensive care units. The issue of major concern while applying these techniques is to ensure appropriate anticoagulation to prevent the clotting of the circuit.

Aim: The aim of this paper is to present regional anticoagulation as a method which is currently used in continuous extracorporeal blood purification techniques.

Material and methods: This work is based on the available literature and the authors' experience.

Results and discussion: Anticoagulation used to prevent the clotting of the circuit in extracorporeal blood purification techniques may be regional or systemic. Regional anticoagulation inhibits clotting only in the extracorporeal circuit. In this case either sodium citrate together with calcium substitution or heparin with protamine sulfate is used. Systemic anticoagulation involves the inhibition of clotting in the extracorporeal circuit and in the patient's body. Regional citrate anticoagulation (RCA) is obtained with the use of citrate. With this technique calcium substitution is necessary in order to prevent hypocalcemia. Other possible complications include alkalosis, metabolic acidosis, hypercalcemia and hypomagnesemia. This paper presents also some practical aspects of regional anticoagulation during continuous renal replacement therapy (CRRT).

Conclusions: The application of RCA has contributed to a wider use of CRRT in intensive therapy units. The greatest advantage of this method is almost complete elimination of bleeding complications associated with the therapy. It enables effective blood purification in the patients in whom the use of heparins is contraindicated. This fact has found confirmation in Kidney Disease: Improving Global Outcomes (KDIGO) guidelines.

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1. INTRODUCTION

Extracorporeal blood purification techniques have been commonly used in intensive care units for many years. What is meant here is not only the classic continuous renal replacement therapy (CRRT), but also the monitoring of intravascular volume in patients without renal dysfunction, albumin dialysis, therapeutic plasma exchange and recently also cytokine elimination. The most important issue to be solved in using all of the techniques mentioned above is to avoid clotting in the extracorporeal circuit. The clotting process is initiated by the contact of blood with surfaces made of artificial materials and with the air present in the deaeration chambers or in the filter if it has not been fully deaerated. Other phenomena which initiate clotting include: hemoconcentration on the filter connected with the filtration process, the change in the character of blood flow to turbulent at the sites where the elements of the circuit vary in diameter and the stoppage of blood flow in the circuit. What should also be mentioned is the activation of the plasma clotting system and platelets as a result of trauma to cellular components of blood occurring in the extracorporeal circuit. Consequently, appropriate anticoagulation is crucial for the achievement of the adequate effectiveness of the implemented procedure.[1]

2. AIM

The aim of this paper is to present regional anticoagulation as a method which is currently used in continuous extracorporeal blood purification techniques, with particular emphasis on the practical aspects of their application. Additionally, its aim is to indicate potential threats and complications associated with the use of this method.

3. MATERIAL AND METHODS

This work is based on the available literature and the authors' experience.

4. RESULTS AND DISCUSSION

Anticoagulation used to prevent the clotting of the circuit in extracorporeal blood purification techniques may be regional or systemic. Regional anticoagulation inhibits clotting only in the extracorporeal circuit. In this case either sodium citrate together with calcium substitution or heparin with protamine sulfate is used. Systemic anticoagulation involves the inhibition of clotting in the extracorporeal circuit and in the patient's body.[1]

4.1. Regional citrate anticoagulation (RCA)

Calcium is clotting factor IV, essential for the process of factor IX and X activation, and is also involved in prothrombin to thrombin transformation. Serum concentration of calcium ions ranges 1.0–1.3 mmol/L. The decrease in the concentration of plasma ionised calcium causes a reduction in the rate of blood clotting process. Blood clotting is significantly impaired below the level of 0.56 mmol/L, while at calcium values below 0.33 mmol/L no blood clot formation is observed.[2–4]

The use of RCA involves decreasing ionised calcium level in the blood within the extracorporeal circuit to the level at which blood clotting does not occur. Calcium level in the extracorporeal circuit is reduced by infusion of sodium citrate, which binds calcium ions, to the line receiving blood from the patient. In order to ensure the decrease in ionised calcium level in the blood below 0.33 mmol/L, the citrate concentration in the blood should reach approximately 4 mmol/L. Before the return of blood from the extracorporeal circuit to the patient, an infusion of calcium chloride or calcium gluconate is connected, directly through a dialysis cannula, to normalise calcium level. It is of critical importance for the restoration of normal blood clotting conditions and avoiding other complications of hypocalcemia. During the dialysis, hemofiltration or hemodiafiltration 50% of citrate is eliminated from the blood in the extracorporeal circuit. The remaining amount of citrate is carried to the patient's blood, where it is metabolised to bicarbonates, among others. It is of note, then, that during citrate anticoagulation, there is an additional supply of bicarbonates. Apart from bicarbonates, together with citrate, an extra load of sodium is supplied to the body. It is for this reason that dialysis and substitution fluids used in the procedures with citrate anticoagulation contain reduced sodium and bicarbonates levels. Dialysis fluids are also free of calcium ions in order to prevent reverse diffusion of those ions from the dialysis fluid to the blood and the activation of the clotting process. This rule is also applied to substitution fluids in predilution.[2–4] During the procedure it is necessary to monitor the level of ionised calcium in the patient's blood and in the blood within the extracorporeal system (with post-filter blood sampling). Due to the fact that the level of ionised calcium in the extracorporeal circuit is very low, it is important that the laboratory performing the tests offers validated tests for calcium level measurements reaching 0.1 mmol/L, which is markedly below the physiological norm.[5]

The citrate used, which is administered into the extracorporeal circuit, may come in the form of hypertonic or isotonic solution. During continuous hemodialysis and postdilutional hemofiltration hypertonic solutions are used, while during continuous hemodiafiltration and predilutional hemofiltration isotonic solutions are used. Postdilutional solutions may either be calcium-free fluids or fluids containing calcium ions, but must always be free of citrate. In order to normalise ionised calcium concentration in the blood calcium chloride or calcium gluconate is administered directly to the patient's vein or into the venous line in the extracorporeal circuit. In order to correct possible metabolic alkalosis citric acid is added to some fluids. This is the cause of an increased incidence of metabolic acidosis.[6] A schematic representation of RCA-CRRT circuit is shown in Figure.

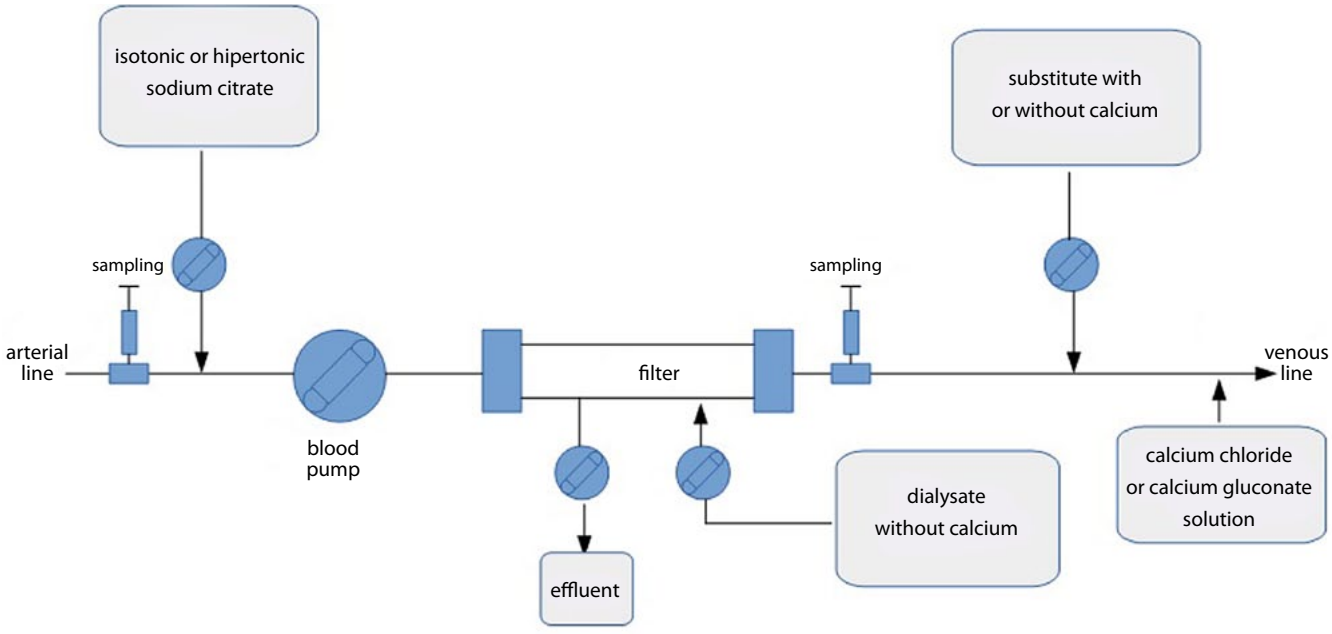

Figure. Schematic representation of RCA-CRRT circuit.

It is of importance that during a procedure involving the use of RCA adequate relations of blood flow, dialysate and citrate solution should be maintained. In order to adequately reduce the calcium ion concentration, the flow of sodium citrate solution must always be adjusted to the volume of the blood flowing. Additionally, the dialysate flow should be set in such a way as to remove the right amount of the calcium citrate. Reducing the dialysate flow in relation to the blood flow results in a greater load of calcium citrate reaching the patient; it is then metabolised to bicarbonates, which leads to metabolic alkalosis. Increasing the flow of dialysate in relation to blood flow, in turn, results in the removal of citrate during the dialysis and a reduced supply of bicarbonates produced in citrate metabolism to the patient. That usually leads to the development of metabolic acidosis due to the fact that in dialysis fluids used in the given method the bicarbonates concentration is lower than its physiological level. The relations described above are the rationale behind developing protocols for the right settings for the flows of blood, dialysate, citrate and the adequate substitution of calcium ions by the suppliers of blood purification technologies.[2–4]

The application of RCA has contributed to a wider use of CRRT in intensive care units. The greatest advantage of this method is almost complete elimination of bleeding complications associated with the therapy, compared with using of heparine. Moreover, an increase in filter lifespan is documented, with a secondary advantage in reaching the prescribed dialysis dose. Additionally, RCA enables an easy and effective blood purification in the patients in whom the use of heparins is absolutely contraindicated, that is: those after cerebrocranial injury, with hemorrhagic cerebral stroke, with multi-organ injury, in early post-operative period, and in the case of heparin induced thrombocytopenia (HIT). Another advantage of RCA is that it facilitates the process of procedure planning, invasive procedures included, as it eliminates the need to wait for the coagulation system to normalise after withholding anticoagulants or to reverse their action, which in many cases is impossible. Moreover, if a need arises, the procedure may be continued during the operation.[1,7,9]

4.2. RCA-related adverse effects

4.2.1. Metabolic alkalosis

Calcium citrate, which leaves the extracorporeal circuit together with blood is metabolised to bicarbonates in the patient's body. Excessive flow of citrates may result in the development of metabolic alkalosis. Therefore it is important to adjust the flow of dialysate and citrate to the blood flow and to use in this case the filters with large surface, that is minimum 1.4 m^2 for an adult patient. During the procedure, despite using the optimal flows and the appropriate filter, the exchange of substances on the filter membrane may be slowed down as a result of microclotting or opsonisation of the membrane with proteins, with retained filter patency. This will cause a reduced removal of calcium from the blood and a greater amount of bicarbonates being produced, which will, in turn, lead to an increase in blood pH. There will also be an increase in the concentration of ionised calcium, produced during the utilisation of calcium citrate, which will necessitate the reduction of its substitution. Blood pH and bicarbonates measurements should be carried out every 8–12 h in order to prevent metabolic alkalosis. If the two parameters rise, the flow of dialysate in relation to the blood flow should be increased by about 20%–30%. Should pH and bicarbonates values continue to grow, the solution is the exchange of the filter or the whole system.[1,8]

4.2.2. Metabolic acidosis

Slowing or inhibition of citrate metabolism results in their accumulation in the patient's blood and leads to the development of metabolic acidosis. Such a situation is ob-

served with the diminishing of cell metabolic potential, that is in a shock or when citrate metabolism is reduced in the carboxylic acid cycle, which is associated with metabolism of another substrate, such as lactates. The reduction of citrate conversion to bicarbonates will lead to the decrease in blood pH. In turn, elevated levels of citrates in the blood will cause a decrease in ionised calcium level, and thus the need to increase its substitution. The effect of this is the rise in total blood calcium and the proportion of total to ionised calcium. Anion gap is also increased. Therefore accumulation of citrate may be recognised when the measured proportion of total to ionised calcium concentrations is higher than 2.5 and the anion gap exceeds the norm. This phenomenon occurs in 1% to 3% of patients undergoing the procedure of blood purification using RCA. So far no other adverse effects of this process have been recognised, except for aggravation of metabolic acidosis.[8,10] The predictive parameters, the occurrence of which significantly increases the risk of citrate accumulation, are now considered to be liver dysfunction, which is the cause of the prothrombin index falling below 26% , and/or lactate level over 3.4 mmol/L. Citrate accumulation is an adverse phenomenon because it exacerbates metabolic acidosis. Consequently, with an increase ratio of total to ionised calcium in the blood above 3, citrate supply should be reduced , with the approved ionised calcium level of 0.4 mmol/L in the extracorporeal circuit. Ineffectiveness of such measures dictates the need to consider changing the anticoagulation method or discontinuing anticoagulation during CRRT. It is very often that clotting disorders in severely ill patients allow to achieve acceptable time of filter longevity without using anticoagulation.[11]

4.2.3. Hipocalcemia

The most common causes of hypocalcemia include insufficient calcium substitution or hypocalcemia which is not CRRT-related. In order to prevent this complication, frequent measurements of ionised calcium levels must be carried out, both in the patient's blood and in the blood from the extracorporeal circuit. In the case of recurrent or prolonged hypocalcemia, particularly when the level of ionised calcium in the blood falls below 0.8–1.0 mmol/L, the secretion of the parathyroid hormone is stimulated and calcium ions are released from the bones. This may result in significant demineralization of the bones and, what follows, a high likelihood of pathological fractures.[1,12]

4.2.4. Hipercalcemia

The accumulation of citrates is manifested by total calcium concentration in the patient's blood exceeding the norm with concurrent normal or decreased level of ionised calcium. Excessive calcium substitution as well as CRRT-unrelated hypercalcemia will lead to the elevation of ionised and total calcium concentrations. The management in each of these cases involves the reduction of calcium substitution.[8]

4.2.5. Hipomagnesemia

This complication may arise during CRRT independently of the type of anticoagulation used, due to – significantly lower than in the plasma – content of magnesium ions in substitution and dialysis fluids containing calcium. Calcium-free fluids used in RCA are characterised by relatively high (approximately 1 mmol/L) magnesium content; however, in this type of blood purification procedure hypomagnesemia may also occur. As it is the case with calcium kations, citrate anions bind to magnesium kations. Despite high concentration of free magnesium ions in the dialysis fluids used, the attached ions undergo elimination in the filter. This phenomenon is the reason why special attention must be paid to the level of magnesium ions in the patient's blood; the concentration of this ion must be measured at least once per day in order to avoid hypomagnesemia and, if there is a need, substitution must be provided.[8]

4.3. Regional anticoagulation in the heparin--protamine sulfate system

Some attempts have been made to reverse the effects of heparin administered to the CRRT extracorporeal circuit using protamine sulfate, basing on the experience of cardiac surgery centres. However, the differences in the half-life of both drugs (30–150 minutes for heparin, 80 minutes for protamine sulfate) made it impossible to develop one uniform protocol for their use in procedures lasting a few days and precluded this management from becoming a part of everyday practice.[13,14]

5. CONCLUSIONS

The application of RCA has contributed to a wider use of CRRT in intensive care units. The greatest advantage of this method is almost complete elimination of bleeding complications associated with the therapy. Additionally, it enables an easy and effective blood purification in the patients in whom the use of heparins is absolutely contraindicated. This fact has found confirmation in Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, which recommend using this type of anticoagulation both in patients with an increased risk of bleeding and those who are free of this risk.[15] On the other hand this method carries the risk which can not be observed when using systemic anticoagulation.[8] This is why doctors working in intensive care units sholud improve their knowledge about this topic.

Conflict of interest

Dariusz Onichimowski declares that he receives fee for lectures about similar subject from Fresenius Medical care. Others authors declare to have no potential conflict of interest.

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