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Review paper

Systemic anticoagulation during continuous renal replacement therapy – practical aspects

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Abstract

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

Aim: The aim of this paper is to present methods of systemic anticoagulation which are currently used in continuous extracorporeal blood purification techniques.

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

Results and discussion: The prevention of clotting in the extracorporeal circuit may be achieved through regional or systemic anticoagulation. Systemic anticoagulation is usually achieved by administration of unfractionated heparin. The most common complications include bleeding; additionally, there is a risk of type II thrombocytopenia occurring. Systemic anticoagulation may also be provided through administration of low molecular weight heparins. Some research papers have discussed the use of thrombin antagonists (argatroban, bivalirudin) and heparinoids (danaparoid, fondaparinux), as well as platelet inhibitors as systemic anticoagulants. It is also possible to conduct extracorporeal blood purification without anticoagulation.

Conclusions: The introduction of continuous extracorporeal blood purification techniques into everyday practice of intensive care units has brought many unquestioned benefits to the patients treated in this setting. On the other hand, it means that doctors need to show an in-depth knowledge of the anticoagulation methods. Despite the wider use of regional anticoagulation during continuous renal replacement therapy, systemic anticoagulation is still important. This is especially when therapies with high blood flow are performed and contraindications to citrate use are present.

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1. INTRODUCTION

Extracorporeal blood purification techniques are widely performed in intensive care units. They can be used as a classic continuous renal replacement therapy (CRRT), but also for the monitoring of intravascular volume in patients without renal dysfunction, therapeutic plasma exchange, albumin dialysis and recently cytokine elimination.[1] Avoiding clotting in the extracorporeal circuit is the most important issue during all of the techniques mentioned above. The clotting process is initiated by the contact of blood with surfaces made of artificial materials and with the air present in the filter if it has not been fully deaerated. Other factors 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. The activation of the plasma clotting system and platelets as a result of trauma to cellular components of blood occurring in the extracorporeal circuit also sholud be mentioned.[2] Consequently, proper anticoagulation is crucial for the achievement of the adequate efficiency of the implemented procedure.[1]

2. AIM

The aim of this paper is to present methods of systemic anticoagulation which are 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 associated with the use of particular types of anticoagulation.

3. MATERIAL AND METHODS

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

4. RESULTS AND DISCUSSION

Regional or systemic anticoagulation can be used to prevent the clotting of the circuit in extracorporeal blood purification techniques. Regional anticoagulation inhibits clotting only in the extracorporeal circuit. Systemic anticoagulation, involves the inhibition of clotting in the patient's body and in the extracorporeal circuit. It may be achieved with the use of unfractionated heparin, low molecular weight heparins (LMWH), thrombin antagonists (argatroban, bivalirudin), heparinoids (fondaparinux, danaparoid) and platelet activation inhibitors.[1–3]

4.1. Systemic anticoagulation using unfractionated heparins

Unfractionated heparin (UFH) is nowadays the most commonly used type of systemic anticoagulation. In our department systemic anticolagulation with both UFH and LMWH had been used from 2004. Till 2009, after that citrate anticoagulation was intruduced. In each year we performed about 500 treatments per person per day. This allowed us to gain some experience in this field. UFH action consists in inhibiting active clotting factors, which in this case are factors XII, XI, X and II, with the most potently inhibited factor being factor II, that is thrombin. No single dosing regimen for heparin has so far been developed for the use during extracorporeal blood purification techniques in patients treated in intensive care units.[2] This results from varied degree of risk for bleeding complications in critically ill patients, as well as individual variability in the response to heparin in this group of patients. The dose of heparin must be adjusted during the procedure in such a way as to maintain the balance between the risk of a life-threatening hemorrhage and the expected clinical effect, which is a long operating time of the extracorporeal circuit. It is considered that 18–24 h is the shortest acceptable time of using the filter in the extracorporeal circuit with UFH used for anticoagulation. The necessity of frequent exchange of the filter or the whole circuit due to its clotting is unacceptable because of excessive blood loss.[4]

When using heparin anticoagulation, the extracorporeal circuit is flashed with normal saline (10,000 U of heparin per 1 L of 0.9% NaCl). Then a loading dose is administered, which is 10–30 U/kg bw; heparin continuous infusion is instituted at 5–20 U/kg bw per hour. Heparin is administered into the arterial line of the extracorporeal circuit (the so called access line). When beginning the procedure one must remember that when two lines of the circuit are simultaneously attached, the patient will receive 200–300 mL of fluid containing heparin dose of about 2000–3000 U. If this type of attachment is chosen, no loading dose is administered.[5]

While using UFH as an anticoagulation method during CRRT its efficacy is monitored by measurement of activated partial thromboplastin time (APTT) at regular time intervals or by means of activated coagulation time (ACT). Blood samples are taken from the venous line. Measured APTT should fall in the range of 45–80 s depending on the risk of bleeding in a given patient. The recommended ACT is 140–180 s in patients after procedures and 200–250 s in patients without the risk of bleeding.[2]

The half-life for heparin is approximately 1,5 h; in practice it falls in the range between nearly 0,5 h and 2,5 h. In renal insufficiency this value may even reach up to 3,0 h.[6] UFH may be removed during renal replacement therapy, which results from its molecular weight of 12,000–15,000 Da. All of this makes pharmacokinetics of heparin difficult to predict, particularly in a severely ill patient undergoing renal replacement therapy. Thus, the decisive factor regarding the effectiveness of the prevention of clotting in the extracorporeal circuit is not the heparin dose but APTT or ACT value.[7] The recommended time to conduct measurements of the coagulation system is the interval of not less than 6 h.

The factor required for the normal action of heparin is the right level of antithrombin III (AT III). When there is no adequate prolongation of ACT or APTT in relation to

the dose of the heparin used, AT III level should be measured. In the case of AT III deficiency the treatment of choice is the substitution of the factor. Substituting AT III in a patient who had previously received a loading dose of heparin may cause a transient complete inhibition of blood coagulation (unmeasurable APTT), significantly increasing the risk of life-threatening bleeding. A safer solution is to measure the level of AT III and to substitute it, if required, before the administration of heparyn.[4]

Theoretically, the optimal anticoagulation is considered to be heparin anticoagulation with APTT values preventing the extracorporeal circuit clotting, while posing a small risk of bleeding at the same time. In practice, each APTT prolongation is associated with the risk of bleeding; thus, no optimal APTT values have been determined. The bleeding complications reported in research papers in most cases occurred with APTT prolonged 2 to 5 times above the range of reference values of 30–40 s, while the frequency of filter clotting decreased with APTT prolonged at least 2 times. The literature reports the frequency of bleeding complications to be 10%–50%, the bleeding-related mortality of 15%, and the risk of bleeding and death growing together with APTT increase.[1,7–10]

Another serious adverse effect which may be seen following heparin use is thrombocytopenia type II (HIT-II). The drop in platelet count occurs between day 5 and 10 following the administration of the first dose of heparin. With cases of previous exposure to heparin this time may be shorter. The drop in platelet count of at least 50% of the baseline value occurs as a result of an immune reaction. There are also cases of the value falling to 30–50 G/L. Patients with the platelet count remaining consistently higher than 150 G/L represent about 10% of the group. In patients who develop HIT II, the risk of severe thromboembolic complications rises by 20%–40%, together with the risk of clotting of the extracorporeal circuit. When HIT II occurs or its risk is elevated, neither fractionated nor unfractionated heparin should be used. In such a case the choice of an alternative method of anticoagulation is recommended.[11] Our experience is similar to that presented above. The main adverse effects was bleeding and early clotting of the circuit.

4.2. Systemic anticoagulation using low molecular weight heparin

Unlike unfractionated heparin, LMWH act by the inhibition of active factor Xa, at the same time having much smaller effect on the inhibition of thrombin activity. There are several advantages of LMWH over UFH. First of all, their capacity to activate platelets is smaller and, what follows, the likelihood of heparin-induced thrombocytopenia is reduced. The action of LMWH is less AT III-dependent, therefore no metabolic effects characteristic of UFH are seen. LMWHs are not devoid of disadvantages, either, which include: a relatively long action time, which is even longer with renal insufficiency, a higher cost of therapy when compared with UFH, lack of an easy way to reverse their action with protamine; the most important issue, however, is no available and low-cost method of monitoring their action, the only possibility being the measurement of anti-Xa activity.[2,4]

To date there has not been much research on the use of LMWH during CRRT.[12–16] Most papers report the efficacy of LMWH in prevention of clotting in the extracorporeal circuit as comparable to the use of UFH; no advantage was found regarding the number of bleeding complications, either.[13–15]

4.3. Systemic anticoagulation using thrombin antagonists (bivalirudin, argatroban)

In patients with a diagnosis of HIT the anticoagulant used is argatroban, a second generation direct inhibitor of thrombin. The efficacy of argatroban as an anticoagulant can be monitored by APTT measurement, and it is metabolised in the liver. To date there have been just a few publications reporting on the use of argatroban during CRRT, instituted primarily due to HIT II.[17] The loading dose was 100 mcg/kg bw, while the maintaining dose was 2 mcg/kg per minute. The target APTT value was 1.5–3.0-fold of upper limit of the normal range. With the diagnosis of liver insufficiency the dose of the medication should be reduced. There is no known antidote to argatroban.

In patients with severe liver insufficiency bivalirudin, instead of argatroban, can be used; the drug is a direct thrombin inhibitor with extrarenal and extrahepatic metabolism. As of date one randomized trial including 10 patients was conducted, which was to assess the effectiveness of using bivalirudin during CRRT and to compare it to that of UFH. The time of filter longevity in the patients was significantly longer, and bleeding or thrombotic complications were seen in neither of the groups.[18] Thrombin antagonists have become quite commonly used in patients with HIT during CRRT.

4.4. Systemic anticoagulation with the use of heparinoids (danaparoid, fondaparinux)

Danaparoid shows primarily anti-Xa activity, and its affinity to antithrombin is low. Following its use in patients with HIT, thrombocytopenia occurred in 5%–10% of the patients. Its disadvantage is a long half-life of the medication, which is 48 h. So far only a few papers have been published reporting the use of danaparoid for anticoagulation during CRRT; one of them mentioned bleeding complications, which occurred in 46% patients despite the fact that the drug was used with the concurrent monitoring of anti-Xa activity (0.4 U/mL).[19]

Fondaparinux is a synthetic heparin analogue showing anti-Xa activity. Following the use of a standard dose of 2.5 mg its time of action is similar to that of danaparoid and equals 48 h, being longer in patients with renal insufficiency. The removal of the drug during CRRT is possible only when high-flux membrane is used. As it is the case with previously mentioned drugs, also the use of fondaparinux during CRRT was the subject of only a few studies carried out on small groups of patients. When using fondaparinux

instead of heparin during CRRT, bleeding complications occurred in 4.2%–16.7% patients, with the normal platelet level maintained and the measured level of anti-Xa activity within the normal range as well. The clotting of the extracorporeal circuit was not observed. The use of fondaparinux and the assessment of its safety in patients with HIT requires further research. The disadvantages include its long half-life and the lack of an antidote.[19]

Due to insufficient research confirming the safety and assessing the use of heparinoids during CRRT, their use should only be considered in patients with HIT when direct thrombin inhibitors are unavailable.[19]

4.5. Systemic anticoagulation using platelet inhibitors

Prostacyclin PGI2 and its derivatives: epoprostenol and nafamostat are platelet inhibitors used as anticoagulant during CRRT. These medications act through inhibition of platelet adhesion and aggregation. Few papers have so far presented the assessment of using platelet inhibitors as a method of anticoagulation during CRRT.[3,16,17] Prostacyclin PGI2 has been used with or without heparin. Using this substance prolongs the longevity of the extracorporeal circuit; it is, however, associated with adverse effects: hypotension, flushing, increased pulmonary shunting of deoxygenated blood. The recommended dose is 2–8 ng/kg bw per minute. No loading dose is administered. The dose of 20 ng/kg bw per minute may cause significant hypotension, resolving after about 20 minutes after discontinuing infusion, and the anticoagulant activity lasts up to 2 h.[8]

Currently there is no recommendation for the routine use of prostacyclin as an anticoagulant during CRRT because of its many adverse effects and difficulty in the precise control of dosing. This method can be considered as an additional anticoagulan in the case of recurrent filter clotting.[20] Using epoprostenol and nafamostat as anticoagulants during CRRT remains in the phase of experimental research.

4.6. Extracorporeal blood purification without anticoagulation

In everyday hospital practice there are patients with contraindications for the concurrent use of heparin and citrates.[4] Such a patient may be a person after multi-organ injury, including craniocerebral trauma, with extremely low oxygen supply to the tissues. Citrates are relatively contraindicated also in patients with circulatory shock, liver failure with or without cirrhosis, severe hypoxemia, and after massive blood transfusion.[22,23] The safest solution in such a case will be conducting renal replacement therapy without anticoagulation. Attention should be paid to the fact, however, that the risk of clotting of the filter is higher. The factors increasing the longevity of the extracorporeal circuit will be: reducing hemoconcentration by using predilution or choosing diffusion techniques, efficient venous access, high blood flow, a thorough deaeration of the filter, flushing the circuit and the filter with normal saline containing heparin before the beginning of the procedure, the measurement of AT III concentration and its substitution, if required.[2,4,24]

5. CONCLUSIONS

The introduction of continuous extracorporeal blood purification techniques into everyday practice of intensive care units has brought many unquestioned benefits to the patients treated in this setting. On the other hand, it means that doctors need to show an in-depth knowledge of the anticoagulation methods. Despite the wider use of regional anticoagulation during CRRT, systemic anticoagulation is still very important. This is especially when contraindications to citrate use are present and therapies with high blood flow are performed.

Conflict of interest

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