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Effect of regional citrate anticoagulation on critical patients with continuous renal replacement therapy

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ABSTRACT

Objective: To investigate the efficacy and safety of regional citrate anticoagulation (RCA) in continuous renal replacement therapy (CRRT) for critical patients. **Methods:** A total of 83 critical patients need CRRT in the intensive care units of our hospital from July 2012 to June 2016 were recruited in the study, and the patients were divided into two groups randomly, the patients in observation group received the RCA treatment, and the patients in control group received traditional low molecular heparin anticoagulation. The difference of safety indicators, biochemical indicators, extracorporeal circulation blood coagulation condition and complications in patients were determined between two groups. **Results:** Compared with control group, the patients in observation group had an elevated level of iCa^{2+}, the level of chloride ion reduced, the use time of filter increased, the bleeding cases reduced, the concentrations of urea nitrogen, creatinine TNF- α , IL-1 β , IL-8 and NO were all significantly downregulated, the data have a significant difference ($P < 0.05$). **Conclusions**: RCA is a safe and effective method for CRRT in patients with a high risk of bleeding.

1. Introduction

Continuous renal replacement therapy (CRRT), a kind of important clinical application in patients with severe treatment, is a kind of renal replacement based on intermittent blood purification treatment sincerely[1]. Clinical pays much attention to CRRT owing to the advantage in hemodynamics and stability *etc*[2]. Nevertheless, big difficult problems faced by the critical patients treated with CRRT treatment clinically are active bleeding, blood coagulation dysfunction at high risk of bleeding condition. Hence extracorporeal circulation of anticoagulant technology is the key procedure to ensure the CRRT turn smoothly and effectively, and it is also one of the most serious challenge facing the CRRT[3–5]. At present, the most commonly used method is to use common heparin or low molecular heparin anticoagulation clinically, but for critically ill patients, many obstacles exist clotting mechanism, and in patients with increasing doses of anticoagulants, the risk of bleeding will increase at the same time, therefore not suitable for the treatment of patients with severe hemorrhagic[6–8]. According to reports, the literature method of regional citrate anticoagulation (RCA) effect is exact, and will not affect the patients of coagulant function, can extend the service life of the filter and improve the biocompatibility, anti-inflammatory and anti oxidative stress effect, and therefore is widely applied in clinical. Also, RCA is preferred to the latest global prognosis of kidney tissue in the guide recommend[9] in the improvement. In this study, we focus on the application of RCA to CRRT. We select severe cases accepting continuous CRRT since 2012 in this hospital in ICU, 43 cases of 83 patients with RCA anticoagulation as observation group, 40 cases as control group using traditional low molecular heparin anticoagulation, to explore the safety and efficacy of anticoagulation method. At last, we discuss the application of RCA in CRRT.

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2. Materials and methods

2.1. Clinical data

A total of 83 severe patients accepting CRRT were selected in our hospital ICU in July 2012 to February 2016. Inclusion criteria: (1) all sign the informed consent; (2) ages 18 to 75; (3) without anticoagulation contraindication; (4) Fluent prognosis ; (5) patients with illness such as AKI in hospitalized, should first give strong heart, diuresis, enlarge the treatment such as blood vessels, without ease immediately began to CRRT; (6) complete information collection.

Exclusion criteria: (1) citrate allergies; (2) the concurrent systemic inflammation infection; (3) liver failure; (4) anticoagulant therapy observation before 12 h, or long-term use of anticoagulants. Patients in the hospital can be divided into two groups according to odevity number. Observation group 43 cases, 25 cases of male and female 18 cases, age was (56.3 ± 17.6) years. Control group 40 cases, 23 cases of male, female 17 cases, age was (55.7 ± 16.8) years.

2.2. Method

2.2.1. CRRT treatment scheme

In the treatment, two groups of patients both used continuous intravenous-venous hemofiltration (CVVH) model in the process, used Aquarius 3.5 CRRT machine (Baxter company) according to the patient's own condition, select multi-flow100 (membrane area of 1.6 m^2) or 18-AC filter scale (membrane area of 1.8 m^2). In addition, the displacement fluid preparation method according to the doctor's advice was based on the condition of the patients with the configuration. The blood flow velocity was 180 mL/min, the displacement fluid speed was 2 000 mL/h, treatment 12-24 h continuously, diluted before input mode.

2.2.2. Anticoagulation method

Observation group: citric acid was inputted through the vessels road with 4% sodium citrate with infusion pump, at rate of 180 mL/h at the start. Meanwhile, peripheral venous 10% calcium gluconate supplement was at a speed of 18-22 mL/h, pump inputted from line to trace vein. The input speed of sodium citrate and calcium gluconate should be constantly adjusted during the treatment process according to the serum and filter free Ca^{2+} level. Adjusting standard after filter was free Ca^{2+} level in 0.2-0.4 mmol/L, the level of serum free Ca^{2+} 0.9-1.2 mmol/L. Control group: aline 1 000 mL plus heparin 50 mg loop filter was used and pipe was pierced before the treatment. Low molecular heparin anticoagulation: from the artery an injection of low molecular heparin sodium anticoagulation 5 000 U was used, at the same time in the process of CRRT, artery blood flow was blocked every 30 min, and washed with the physiological saline 100-200 mL in front of the filter. Blood samples were obtained appropriately according to patients' condition, the indicators were observed, progress of CRRT and patients' safety was ensured.

2.3. Monitoring indicators

2.3.1. Citrate anticoagulation of safety index

iCa^{2+}, pH value, Cl^-, Na^+ level and filter using time and so on were monitored and compared.

2.3.2. Extracorporeal circulation blood coagulation condition detection

Coagulation condition evaluation was confirmed according to the appearance of the filter changes, blood clotting was divided into four classes. A total of level 0 represented filter blood coagulation or blood coagulation only emerged several fibers; Ⅰ level blood filter: several fiber clotting, but not more than half; Ⅱ level on behalf of the clotting of blood filter fiber more than half; Level ⅢI: basic is covered in blood clotting, blood filter need to be replaced intravenous crowd to continue treatment. The higher the level was, the more serious the blood coagulation.

2.3.3. Blood index observation

Automatic biochemical analyzer (roche DDP/E702) was used to monitor the two groups blood urea nitrogen (BUN), creatinine (Scr) content changes before and after treatment; ELISA kits was used to examine haemal tumour necrosis factor α (TNF- α), interleukin-1 β (IL-1 β), interleukin 8 (IL-8) and endothelium derived vasodilatation factors (nitric oxide, NO) concentration changes.

2.3.4. Observation of complications

Anticoagulant main complications, including low calcium and folic acidosis, metabolic alkalosis, high sodium and low magnesium levels, *etc*. were observed, and abnormal sensation, such as face and mouth weeks coma, convulsions, and low blood pressure, and so on were also observed.

2.5. Statistical analysis

Data were analyzed with SPSS 19.0, measure data were presented by mean±standard deviation, data between group were compared by *t* test, $P<0.05$ indicated that difference was statistically significant.

3. Results

3.1. Citrate anticoagulation of safety index

iCa^{2+} level of observation group was significantly higher than that of control group ($P<0.05$), Cl^- level was lower than the control group ($P<0.05$), the use of filter time was longer than that of control group

Table 1
Safety indicators comparison.

Groups	*n*	iCa^{2+} (mmol/L	Cl^- (mmol/L)	Na^+ (mmol/L)	pH value	Time of filter usage (h)
Observation group	4	2.31±0.37*	92.56±8.13*	137.51±12.59	7.40±0.07*	21.62±3.02*
Control group	4	1.87±0.25	110.45±10.24	138.20±13.12	7.38±0.09	15.36±2.70

Note: * compared with controls, $P<0.05$.

($P<0.05$); Differences in Na^+ level and pH value were not statistical significant ($P>0.05$), as shown in Table 1.

3.2. Comparison of blood bleeding and anticoagulant effect

There were 2 cases with bleeding or bleeding from the original increase of observation group (4.7%) and 8 cases in control group (20.0%); There were 1 cases with 0-Ⅰ level (2.3%), no patients with clotting Ⅱ-Ⅲ level, 7 cases (17.5%), 3 cases (7.5%) respectively in control group.

3.3. Scr and BUN level comparison

Scr, BUN levels in observation group were significantly lower than control group ($P<0.05$), as shown in Table 2.

Table 2
Scr, BUN level comparison.

Groups	*n*	Scr (μmol/L)	BUN (mmol/L)
Observation group	43	166.3±31.5*	15.7±4.1*
Control group	40	310.3±47.8	29.8±6.4

Note: * compared with controls ($P < 0.05$)

3.4. Two groups comparison of patients with TNF-α, IL-1β, IL-8 and NO levels

The TNF-α, IL-1β, IL-8 and NO levels of the observation group of patients were significantly lower than control group ($P < 0.05$), the results are shown in Table 3.

3.4. Complications compared

There were no serious complications occurred.

4. Discussion

CRRT is one of the most effective blood purification in critically ill patients with emergency measures, its advantage lies in the ability to maintain the body capacity balance, correct electrolyte disorder and remove harmful cell factor, *etc*.; So the application in the clinical of CRRT replace the damaged kidney function has been widely used[10]. During the process of CRRT, due to frequent clotting and replace pipeline filter, it is likely to lead to blood loss and reduce treatment time, thus increase the cost of treatment; Whereas excessive anticoagulant will lead to the cure bleeding seriously, severe cases are likely to endanger the life, so the anticoagulant technology is one of the important measures to ensure CRRT smoothly and effectively worked, it is also one of the main challenges faced by CRRT. Clinically, the traditional way is basing on the ordinary heparin or low molecular heparin to systemic anticoagulation, but it may be not suitable for patients with high risk bleeding tendency for probably increasing the risk of bleeding[11-13].

As a new type of anticoagulation, RCA is a hot spot in clinical at present. For the method of mechanism, the patient's blood is derived *in vitro*, input at the arterial end of sodium citrate, and in extracorporeal circulation. During the process, folic acid group complexed with the blood iCa^{2+} in filter, resulting to the form of soluble and difficult dissociation calcium citrate. The iCa^{2+} levels dropped in extracorporeal circulation, inhibits prothrombin trans into thrombin, further preventing blood coagulation process, leading to anticoagulant effect *in vitro*. As an excellent way to solve the hemorrhage patients at high risk of CRRT anticoagulation problems[14,15], RCA is simple, safe, effective, and does not increase the risk of bleeding in patients, and will not affect the body's blood coagulation. Besides, a recent study found that RCA[16] has been gradually applied in clinical practice owing to the prolong service life of RCA filter. The time of filter using was obviously prolonged when RCA anticoagulant comparing the traditional of heparin anticoagulation ($P<0.05$), and the security indexes and blood biochemical indicators show the superiority, namely the RCA effect affirmatively. Therefore, RCA has extensive research and application value according to the patients with clinically severe CRRT treatment process.

To sum up, by comparing the application of RCA with the

Table 3
Blood biochemical indexes comparison.

Groups	*n*	TNF-α (ng/L)	IL-1β (ng/L)	IL-8 (ng/L)	NO (μmol/L)
Observation group	4	956.2±245.*	654.8±162.8*	387.3±96.8*	94.1±27.1*
Control group	4	1 524.4±615.1	723.1±134.4	444.1±121.8	102.2±31.4

Note: * compared with controls, $P<0.05$).

traditional technique of heparin anticoagulation for patients at high risk of bleeding CRRT, RCA method is safe, effective and feasible, not adding to the patient's bleeding tendency, but will not cause significant effect to coagulation mechanism for patients. So, it is a pivotal way of clinical significance of anticoagulation.

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