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CLINICAL PHARMACOLOGICAL APPROACH TO THE USE OF DRUGS AFFECTING HEMOSTASIS IN CHILDREN

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Abstract:

The paper examines the safety and efficacy of using a domestic hemostatic agent, recombinant activated factor VII, coagulagil VII, and prothrombin complex concentrate, prothromplex-600 (Baxter, Austria), in neonatal and pediatric cardiac surgery. The study included 56 children aged 7 days to 5.5 years, who underwent artificial circulation surgery for congenital heart defects. Clinical and laboratory data indicate that coagulagil VII and prothromplex-600 are effective in stopping bleeding.

Keywords: Bleeding, prothrombin complex concentrates, recombinant activated factor VII, cardiac surgery, artificial circulation.

INTRODUCTION

Bleeding in cardiac surgery remains a fairly common and serious complication, often leading to the development of multiple organ failure (MOF) and increased mortality. Preoperative administration of anticoagulants, heparinization, activation of fibrinolysis, destruction of platelets during artificial circulation (AC), long sutures on the main vessels and heart chambers are the most common causes of bleeding in cardiac surgery. During surgical correction of congenital heart defects (CHD) in newborns and young children (1–3 years), whose body weight often does not exceed 15 kg, there are several more factors that aggravate the risk of blood loss.

MATERIALS AND METHODS

One of these factors is hemodilution associated with CPB. Due to the small circulating blood volume (CBV) in children, the primary filling of the extracorporeal circuit ("prime") is comparable to the CBV of the child or even often exceeds it. Despite the predominant use of fresh frozen plasma (FFP) and donor erythrocytes, there is a deficiency of coagulation factors in the primary filling volume of the CPB apparatus. The immaturity of the hemostasis system in the newborn and the concomitant deficiency of coagulation factors often lead to increased bleeding, which is confirmed by a decrease in the frequency of postoperative bleeding as the child reaches older age [1–3]. Our examination of children with cyanotic type CHD [4], confirmed by literature data [5], revealed a deficiency of prothrombin complex factors, antithrombin III, proteins C and S, and a pronounced disturbance of blood rheology, which leads to an imbalance in the hemostasis system and an increased risk of both hemorrhagic and thrombotic complications in the postoperative period.

RESULTS AND DISCUSSION

Critical heart defects of the neonatal period, requiring urgent surgical intervention under conditions of hypothermia and circulatory arrest, also predispose to the development of hemorrhagic complications. Technical features in most cases do not allow the surgeon to perform additional surgical hemostasis after completion of the main stage of the operation, for example, during correction of transposition of the great arteries or in case of hypoplastic left heart syndrome (Norwood operation), etc. In recent years, the population of children who undergo repeated interventions on the "open" heart at the age of 1 to 5 years has increased. The body weight of such children does not exceed 10–15 kg and dilution of coagulation factors during CPB remains relevant for them, and the risk of bleeding increases due to the huge wound surface formed as a result of repeated surgical access to the heart and great vessels. Thus, postoperative correction of the hemostatic system is a serious problem in cardiac surgery of newborns and young children, one of the solutions to which may be the use of concentrated or recombinant blood coagulation factors. The advantages of their use compared to FFP are a dose-dependent effect, a small volume of administered fluid, a high concentration of factors/coagulation factor, rapid preparation of solutions for infusion, the possibility of storage at room temperature, administration without preliminary defrosting and determination of the blood group, the absence of post-transfusion complications (post-transfusion acute lung injury, etc.). In conditions of ongoing bleeding in a small child, it is important that the time until the implementation of the hemostatic effect when administering drugs to correct hemostasis is significantly less than when using FFP [2]. Currently, the blood products available for use are recombinant activated coagulation factor 7 (rFVIIa), or coagul-VII-eptacog-alpha [3], which is an analogue of the drug

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Novo-Seven [8], and prothrombin complex concentrates (PCC), in particular prothrombin-600, which includes not only prothrombin complex factors, but also anticoagulants - antithrombin, heparin, protein C [4].

An assessment of the clinical efficacy of rFVIIa allowed us to conclude that bleeding was stopped in 94% of children. A dose of 100 mcg per 1 kg of patient weight was sufficient to stop bleeding. Diffuse bleeding that developed in one patient could not be corrected by the drug and required resternotomy. In another case, an additional dose of the drug (100 mcg/kg) was required. For laboratory assessment of the "prime", a study of the level of blood coagulation system parameters was performed. Low fibrinogen content, ATIII, prolongation of INR, APTT were detected.

In all cases of rFVIIa (coagul-VII) use, a decrease in the bleeding rate was noted up to achieving a "dry surgical wound". There were no thromboses or allergic reactions associated with the use of the drug in the perioperative period, which is consistent with the data of other authors [5].

According to the coagulogram data, the most informative indicator for assessing the hemostatic effect of the drug used was the prothrombin time indicator – international normalized ratio (INR), which statistically significantly decreased ($p = 0.01$) after the introduction of rFVIIa. The APTT and fibrinogen indicators did not change ($p > 0.05$). The hemoglobin and hematocrit levels at the end of CB were 100 g/L and 30%, an hour after the introduction of the drug, hemoglobin increased to 113 g/L, hematocrit – to 34%. By the 1st day after the introduction of the drug, the hemoglobin level was 118 g/L, hematocrit – 36%. The platelet count at the end of CPB was 123 · 109/l and 110 · 109/l an hour after drug administration, and 105 · 109/l after 24 hours.

According to the thromboelastogram (TEG), after administration of activated factor VII, the blood thickening index (BT), the change in which is due to the level of blood coagulation factors, significantly decreased. The clot formation time (CFT) remained extended, with only a tendency for it to shorten after drug administration. The clot density (MCF) was within the reference values.

The presented data indicate a statistically significant reduction in prothrombin clotting time, which in INR units was 1.5 (1.4; 1.6) and 1.1 (1.0; 1.3), respectively. Before the administration of the drug, APTT was 33.5 (31.3; 53.9) s; after the administration, APTT was 35.3 (32.4; 52.3) s.

During the operation, a decrease in the activity of natural anticoagulants was revealed. After hemostatic therapy with the prothromplex-600 CPC, protein C activity increased from 63.0 (41.0; 69.0) to 103.0 (98.0; 118.0)%, and protein S activity increased significantly from 57.0 (49.0; 74.0) to 97.0 (85.0; 120.0)%. Antithrombin activity increased from 78.0 (75.0; 80.0) to 84 (76; 94)%. In children in both groups, hemodynamic parameters at the time of drug administration corresponded to the age norm and the nature of the surgical intervention: average blood pressure 55 (42; 65), heart rate 123 (105; 150), central venous pressure 7 (4; 12). The rhythm was sinus or imposed by a pacemaker. Neither Coagil nor CPC had a significant effect on hemodynamic parameters and heart rhythm. According to the data obtained, Coagil-VII at a dose of 100 mcg per 1 kg of patient body weight is an effective hemostatic drug in newborns and children operated on for CHD. Drug administration did not cause changes in hemodynamics, an increase in temperature, and no allergic reactions were noted. Coagil-VII did not significantly change laboratory parameters, with the exception of clotting time in the coagulogram and TEG. No thromboses associated with the administration of the drug in the perioperative period were identified.

CONCLUSION

These drugs should be used with caution when creating intersystem anastomoses, due to their small diameter and low blood flow rate in them. Given the existing imbalance in the hemostasis system and the compromised anticoagulant link in re-operated children with cyanotic defects, they can be a target group for the use of CPC drugs containing anticoagulant components.

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