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SMALL-VOLUME RESUSCITATION FROM TRAUMATIC SHOCK WITH GEKOTON

Abstract. *The article deals with the use of the infusion agent Gekoton (Yuria-Pharm, Ukraine) for small-volume resuscitation in patients with polytrauma and severe traumatic shock.*
Key words: *Gekoton, infusion therapy, polytrauma, traumatic shock, intensive therapy.*

The major task faced by intensive therapy of traumatic shock is to restore the deficit in circulating blood volume (CBV) by means of infusion therapy characterized by adequate composition, volume and rate of infusion. This is due to the fact that the effectiveness of mechanisms maintaining adequate oxygen transport to human tissues in the setting of low blood oxygen levels is first of all dependent on maintaining normovolemia and cardiac contractile activity. Hypovolemia reduces the compensatory effect of low blood viscosity on venous return and depressed myocardial function, thus preventing an increase in stroke volume resulting from increased venous return [1; 2].

Particularly promising in this context seems the strategy of small-volume resuscitation developed to correct acute hypovolemia and based on the use of hyperosmotic crystalloid solutions. The key concept of small-volume resuscitation is producing impact on microcirculation and obtaining immediately improved central hemodynamic responses in patients with severe hypovolemic shock administered only 4 mL of infusion fluid per kilogram.

The use of hypertonic sodium chloride solution for treating hypovolemic shock was first suggested back in 1944. Following that, I.T. Velasco et al. (1980) conducted experiments in dog models with severe hemorrhagic shock and managed to demonstrate that the use of isotonic crystalloid solutions to restore blood volume after blood loss resulted in 100% lethality in the animal models. At the same time, infusion of 7% sodium chloride solution, with 4 mL of infusion fluid administered per kilogram, led to an increase in systemic pressure and restoration of cardiac output with 100% survival rate in the animal models. The same year, J. de Felippe et al. published the results of a clinical study of the use of 7.5% sodium chloride solution given in 100–400 mL doses to 12 patients with severe hypovolemic shock refractory to conventional therapies. The authors registered a rise in arterial pressure and diuretic response; with 9 surviving patients in this group [3]. The studies above laid the foundation of the concept of small-volume resuscitation as a method of initial emergency treatment of hypovolemic shock based on rapid infusion of a small volume (4 mL/kg) of 7.2%–7.5% sodium chloride solution. The effect is due to rapid mobilization of endogenous fluid across an osmotic gradient to the intravascular space [3]. For instance, the infusion of 100 mL of 7.5% sodium chloride solution increases the intravascular volume by 270 mL [4]. The recommended dose of 7.5% sodium chloride solution constitutes 4 mL per kg of body weight; the dose should be infused over 2–5 minutes. The maximum effect – increasing the volume by 8–12 mL/kg – is achieved immediately after the infusion. Other positive effects of administering hypertonic sodium chloride solution include: reduced risk of pulmonary edema due to limited volumes of infused fluids, increased myocardial contractility directly correlated with reduced cellular edema, natriuretic effect

(i.e. reduced sodium reabsorption), corrected intracranial hypertension [4; 5].

Contraindications to administering hypertonic solutions include dehydration, renal failure, plasma hyperosmolarity (>300 mOsm/L), hypernatremia (>150 mmol/L), severe heart failure, uncompensated diabetes mellitus [4]. It should be emphasized that the infusion of 7%–7.5% sodium chloride solution is safe, while the infusion of hypertonic (>10%) sodium chloride solution into a peripheral vein produced a distinct hemolysis [3].

It is important to point out that the infusion of hypertonic sodium chloride solution has a short-term hemodynamic effect. The short-term hemodynamic effect that is caused by a sharp increase in plasma osmolarity is due to the fact that hypertonic solution undergoes rapid and even distribution between extracellular and intracellular sectors. That led to the idea to combine hypertonic crystalloid solutions with colloids, which contributes to the synergistic effect of both hyperosmotic and oncotic components, increases the hemodynamic effect and prolonged action of the medicinal product. A combined use of colloids and hyperosmotic crystalloids brings central hemodynamic parameters within normal range, restores microcirculation and oxygen extraction without significant elevations of blood plasma osmolarity in hypovolemic shock, and lowers intracranial pressure in patients with traumatic and nontraumatic cerebral edema. On the whole, most publications do not register severe hypernatremia after infusions of hypertonic solutions [4].

Importantly enough, small-volume resuscitation presupposes returning the 'borrowed' interstitial fluid through a subsequent infusion of isotonic crystalloid and/or colloid solutions, as the technology allows rapid restoration of a severe deficit in circulating blood volume aimed at stabilizing the patient with severe traumatic shock and saving the patient's life. Therefore, instead of repeat infusion of hypertonic solution which must be avoided, it is crucial to start rehydration therapy using standard plasma substitutes.

The original idea of combined use of hyperosmotic crystalloids with a modern colloid based on low-molecular-weight hydroxyethyl starch (HES 130/0.4) – its advantages proved in a number of research papers [6] – has been developed by the Yuria-Pharm corporation. A significant feature of the resulting medicinal product is its realization of the concept of an infusion medium with balanced electrolyte content [7]. Therefore, Gekoton is a balanced multicomponent hyperosmolar colloidal solution. The active ingredients of Gekoton are: 5% HES 130/0.4 (5.0 g), xylitol (5.0 g), sodium lactate (1.5 g) and electrolytes (NaCl – 0.8 g, KCl – 0.03 g, CaCl – 0.02 g, MgCl – 0.01 g).

The **objective** of this research is to study the effectiveness and safety of using the Ukrainian-produced balanced hyperosmolar colloidal solution Gekoton (Yuria-Pharm, Ukraine) for small-volume resuscitation in patients with polytrauma and severe traumatic shock.

Materials and methods

A total of 40 patients diagnosed with polytrauma participated in the study. All the patients were provided with emergency services in the intensive care unit of the hospital admission department, and subsequently transferred to the resuscitation and intensive care department for polytrauma patients of the Municipal Institution "Dnipropetrovsk Regional Clinical Hospital named after I.I. Mechnikov". All the patients were aged between 25 and 60 years and had the clinical picture of III-IV degree traumatic shock. The patients participating in the study had the systolic arterial pressure (SAP) of ≤ 80 mm Hg and the empirically estimated blood loss of over 1500 mL. The patients were split into two groups: Group 1 being the main group (n = 20) administered Gekoton in the dose of 5–7 mL per kg of body weight as part of the correction scheme for CBV deficit aimed at hemodynamic stabilization; Group 2 being the control group (n = 20) provided with Refortan infusions (HES 200/0.5) in the dose of 5–7 mL per kg of body weight. The patient groups above were clinically representative samples with similar gender and age characteristics (table 1). The assessment of the effectiveness of the method was based on hemodynamic parameters: systolic arterial pressure (SAP), diastolic arterial pressure (DAP), cardiac contractility.

Table 1. Patient characteristics in study groups and patient distribution according to the type of treatment

Parameter	Group 1 (n = 20)	Group 2 (n = 20)
Type of treatment	Conventional therapy + Gekoton	Conventional therapy + 6% Refortan
Age, years	40,3 ± 1,2	41,1 ± 0,7
Body weight, kg	78,5 ± 2,4	80,6 ± 2,1
Male/female correlation, n	15/5	18/2
Blood loss, mL	2600 ± 620	1850 ± 370

The study was conducted in 4 stages: initially, 15, 25 and 40 minutes after infusing Gekoton and Refortan solutions. It should be pointed out that adjunctive vasopressor support in both groups was only used 40 minutes from the moment the medicinal products were infused, and therefore did not influence the assessment of hemodynamic parameters. The patients requiring an earlier use of adjunctive vasopressor therapy were excluded from the study.

Additionally, 24 and 48 hours after the infusion, the patients were assessed for daily diuresis, blood plasma osmolarity, side effects and use of vasopressor support.

All patients in both study groups received a conventional complex of intensive therapy pursuant to the local Clinical Protocol of diagnostic measures and intensive therapy for polytrauma patients adopted by the Clinic of Anesthesiology and Intensive Care, Municipal Institution «Dnipropetrovsk Regional Clinical Hospital named after I.I. Mechnikov». The Protocol includes ABCDE patient assessment, spiral computed tomography considered to be the "gold standard" for diagnosing polytrauma, ultrasound and X-ray examinations, empirical assessment of the degree of blood loss, provision of punctured venous access by means of inserting large-diameter venous catheters (min. 1.4 mm, sizes 14–16–18 G) into 2–3 peripheral veins. In case it is impossible to access peripheral veins and there are respective indications, it is necessary to provide central venous access. Until definitive hemostasis, the target systolic blood pressure is to be maintained from 80 to 110 mm Hg, mean arterial pressure (MAP) – from 60 to 80 mm Hg. It is crucial to make sure that MAP values do not drop below 40 mm Hg, to prevent the development of severe hypoperfusion syndrome causing polyorganic deficiency syndrome and irreversible fatal consequences. High-risk circumstances or continued bleeding call for applying the strategy of permissive hypotension when short-term hypotension (systolic arterial pressure within the range of 80–90 mm Hg) is maintained until surgical hemostasis.

The local Protocol does not recommend using a single hematocrit (Ht) measurement as an isolated marker for bleeding. Instead, it recommends using dynamic Ht measurements and comparing hematocrit values with the clinical picture. It is important to take into account the fact that during the first 1.0–1.5 hours after trauma, hemoglobin levels are not informative due to centralization of blood circulation; they can be within the normal range or in the low normal range.

Patients with traumatic shock that is not corrected by the infusion of 2 L of crystalloid fluid are recommended to undergo early empiric blood transfusion which should take into account not only hemoglobin (Hb) levels, but also each patient's individual physiological parameters, rate and estimated volume of ongoing hemorrhage. The early empiric blood transfusion should be started at Hb < 100 g/L in the setting of ongoing hemorrhage. In the absence of ongoing hemorrhage, blood transfusion should be started at lower hemoglobin levels: Hb ≤ 70 g/L, and with a severe cardiac pathology comorbid with traumatic shock – at Hb ≤ 80 g/L. The mean hematocrit value is 0.30 L/L.

The strategy we employed is based on the earliest possible administration of fresh frozen plasma (FFP) in patients with massive hemorrhage or marked coagulopathy (prothrombin time or activated partial thromboplastin time (APTT) being over 1.5 times the normal value). The initial FFP dose constituted 15 mL/kg, with subsequent dosing being adjusted based on monitored blood coagulation and amounts of other blood preparations.

In the setting of massive blood loss, the ratio of FFP and packed red blood cells was 1:1.

Tranexamic acid in the dose of 1 g was admini-stered through intravenous bolus injection, followed by continuous intravenous infusion (through a perfusor) for > 8 hours.

Cryoprecipitate was administered to patients with persistent bleeding accompanied by fibrinogen deficit with its level being < 1.5-2.0 g/L. Prothrombin complex concentrate is recommended for promptly reversing the effect of peroral vitamin K antagonists, or as an alternative to cryoprecipitate.

Fentanyl is the "gold standard" for induction of anesthesia in polytrauma patients, administered both through bolus injection and continuous infusion through a perfusor.

The major criteria of a patient's recovery from traumatic shock are an induced diuretic response (mean diuretic value > 0.5 mL/kg/hr), and normalized values of acid-base balance (by Ph level and base deficit).

Statistical analysis of the results of the study was carried out using the biometric methods realized in Excel-2003 and Statistica 8.0 software packages.

Results and discussion

As demonstrated by Tables 1 and 2, initially the main study group (administered Gekoton) was predominantly composed of patients with more severe polytrauma, with injuries of higher severity and a higher blood loss which resulted in their more pronounced hypotension. Arterial pressure in Group One was registered between 40/0

and 60/20 mm Hg, cardiac contractility – at 130–140 beats per minute, which indicated an urgent need for antishock measures as such critically low hemodynamic parameters could interfere with the patient's stabilization due to a high possibility of failure to reach the required rate of infusion therapy for restoring the deficit in circulating blood volume and could therefore cause a circulatory collapse in the setting of severe acute hypovolemia.

Due to their inadequate external respiration, the patients in both groups underwent initial intubation and artificial pulmonary ventilation. In the setting of hemodynamic instability, all the patients in Group One and 17 patients in Group Two were provided with vasopressor support (table 1). In a number of cases that was necessitated not only by severe hypovolemia, but also by a severe craniocerebral injury, as well as by the need to maintain optimal cerebral perfusion pressure.

As demonstrated by the analysis of hemodynamic parameters in the patient group administered Gekoton, the patients displayed a tendency to a reduced rate of cardiac contractility and increased systolic and diastolic pressure as soon as within 15 minutes after Gekoton infusion. Within 40 minutes after the infusion, Group One displayed a reliable reduction in cardiac contractility. Similar dynamics were registered in the values of systemic pressure. Within 40 minutes of the therapy, the patients' systolic arterial pressure ($P < 0.05$) and diastolic arterial pressure ($P < 0.05$) were reliably higher compared to their initial values, which testified to high effectiveness of the medicinal product in treating acute blood loss and performing prompt volemic resuscitation (table 2).

Patient Group Two, in contrast to the main group, though demonstrating higher initial levels of arterial pressure (related to a lower volume of blood loss), only displayed a tendency to increased systemic hemodynamic parameters and a reduced rate of cardiac contractility.

24 and 48 hours of the study did not display significant differences in values of blood plasma osmolarity in both groups (table 3). Therefore, the hyperosmotic solution Gekoton did not cause significant changes in the patients' blood osmolarity.

In the patient group administered Gekoton, diuresis remained within normal range 24 hours from the moment of infusion and tended to increase 48 hours from the moment of infusion (table 3), which – based on the absence of cases of acute renal failure – proves the safety of the infusion medium under study.

None of the patients receiving the infusion solutions under analysis displayed any adverse effects. The patients displayed good tolerance to Gekoton infusion. We also registered improvements in the clinical course of trauma related disorders.

Another promising area of using Gekoton is correcting intracranial hypertension (IIH) in patients with severe traumatic brain injuries. For instance, we used Gekoton for patient R (ATO participant) diagnosed

Table 2. Changes in hemodynamic parameters (M ± m)

Parameter	Group	Stage			
		Initial	15 minutes after the infusion	25 minutes after the infusion	40 minutes after the infusion
Cardiac contractility, b/min	I	132,7 ± 4,1	108,4 ± 5,2	96,5 ± 4,8	92,8 ± 6,4*
	II	118,3 ± 4,8	115,0 ± 4,2	114,2 ± 5,6	110,1 ± 6,9
SAP, mm Hg	I	64,2 ± 5,4	92,1 ± 7,6	105,4 ± 6,7	116,9 ± 7,5*
	II	76,0 ± 8,3	84,6 ± 10,9	82,0 ± 10,2	86,9 ± 11,7
DAP, mm Hg	I	38,6 ± 5,6	54,9 ± 6,1	62,1 ± 4,5	72,6 ± 5,9*
	II	49,1 ± 9,3	52,3 ± 8,7	58,7 ± 6,2	69,8 ± 8,4

***Note: validity of differences with initial parameters is $p < 0.05$.**

Table 3. Dynamics of safety and effectiveness parameters of the medicinal products under study (M ± m)

Parameter	Group	Stage	
		24 hours after the infusion	48 hours after the infusion
Diuresis, mL/day	I	1540 ± 368	1860 ± 156
	II	1450 ± 428	1780 ± 280
Osmolarity, mOsm/L	I	294 ± 10	291 ± 6
	II	288 ± 4	286 ± 5
Vasopressors used, n	I	20	14
	II	17	15
Adverse reactions, n	I	0	0
	II	0	0

with gunshot penetrating bullet wound to the head, gunshot wound to left lung, left hemothorax (a condition after left lung resection and drainage of pleural cavity), comminuted gunshot right shin fracture, gunshot bullet wound to the spine at Th 5 vertebral level with spinal cord injury (a condition after laminectomy surgery, hematoma removal and brain detritus). Within 5 days after being wounded, the patient developed negative neurological symptoms, his neurological status deteriorating to 1st degree coma. The results of spiral computed tomography of the patient's brain revealed signs of cerebral edema with an 8 mm displacement of midline structures.

With a view to correcting his intracranial hypertension, the patient was administered a single 400 mL Gekoton infusion. 30 minutes after the infusion the patient displayed positive neurological symptoms with his neurological status improving to deep stupor. Following that, the patient regained full consciousness and was transferred from the resuscitation and intensive care department to a specialized hospital department of his profile.

In conclusion, it is important to mention that effective correction of the volume status in the setting of hypovolemia allows to prevent inadequate tissue perfusion and reduced oxygen transport to tissues. In cases of severe hypovolemia, it leads to hypovolemic shock, thus causing cell damage, polyorganic insufficiency and death. The primary purpose of infusion therapy is to restore adequate circulation with sufficient arterial pressure and cardiac output, thus providing tissue perfusion and oxygenation. Volume therapy in hypovolemia must not only correct systemic hemodynamic parameters, but also improve microcirculation, perfusion and tissue oxygenation. Therefore, in an emergency which requires the use of a small-volume infusion in order to restore the deficit in circulating blood volume, as well as microcirculatory blood flow, Gekoton proves to be a safe and effective infusion agent for small-volume resuscitation of severe hypovolemia in patients with traumatic shock.

Conclusions

1.Gekoton (Yuria-Pharm) as a broad spectrum blood plasma substitute is a safe and effective agent for small-volume resuscitation which along with other antishock measures in patients with polytrauma offers fast treatment for critical hypovolemic condition, ensures hemodynamic stabilization and restoration of CBV deficit with crystalloid and colloid infusion media, thus preventing irreversible shock and improving the outcome in patients with traumatic shock of degrees 3 and 4.

2. Of considerable interest is further study of the use of Gekoton for correcting intracranial hypertension in neurological patients who undergo intensive care.

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МАЛООБ'ЄМНА РЕСУСЦИТАЦІЯ ПРЕПАРАТОМ ГЕКОТОН ПРИ ЛІКУВАННІ ТРАВМАТИЧНОГО ШОКУ

Резюме. Стаття присвячена використанню інфузійного препарату Гекотон («Юрія-Фарм», Україна) для малооб'ємної ресусцитації у пацієнтів із політравмою та травматичним шоком тяжкого ступеня.

Ключові слова: Гекотон, інфузійна терапія, політравма, травматичний шок, інтенсивна терапія.

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LOW-VOLUME RESUSCITATION WITH GECOTON IN THE TREATMENT OF TRAUMATIC SHOCK

Summary. The article deals with the use of infusion agent Gecoton («Yuria-Pharm», Ukraine) for low-volume resuscitation in patients with polytrauma and severe traumatic shock.

Key words: Gecoton, infusion therapy, polytrauma, traumatic shock, intensive therapy.