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ALBUMINOTHERAPY AND HEPARINOTHERAPY RESISTANCE IN EXTENDED ENTERO-MEZENTERIC ISCHEMIA (CLINICAL CASE)

NICOLESCU CRISTIAN MIRCEA[1,2], NICOLESCU LAURA[1,2], TURLE LAVINIA[1], PANTEA VETURIA ELISABETA [1,2] , MOLDOVAN SILVIU[2] , POP ALEXANDRU[1], DAMIAN GRATIAN[1]

[1] „Vasile Goldis" West University of Arad,
[2] Arad County Emergency Hospital

ABSTRACT. We present a case for a patient, age 82, for which a surgical emergency intervention was undertaken, preoperative diagnosis was acute occlusive abdomen. Surgery revealed extended intestinal loop necrosis patient went enlarged enterectomy. After surgery heparin is administered, 5000IU initially bolus, then slow continuous intravenous using the injectomat, the administered doses requiring continuous incremental increases to get the hypocoagulation desired status. After 48 hours from starting treatment, the phenomenon of resistance to heparin was considered, intervention with fresh frozen plasma (without stopping the heparin therapy) was undertaken, afterwards patient evolution being subsequently favorable both in terms of clinical condition and laboratory data.
KEYWORDS: heparin, antithrombin III, activated prothrombin time, albumin

INTRODUCTION

Entero-mesenteric infarction is a form of acute mesenteric vascular insufficiency, is a major abdominal emergency. The triggering element is the mesenteric arterial and/or vein traffic obstruction. Expansion of intestinal necrosis, secondary to vessel obstruction, depends on the segment where the obstruction occurred.

Secondary obstruction lesions range from reversible (ischemic only) to irreversible lesions (necrotic) evolving towards septic shock with abdominal starting point. Extensive necrosis in this case (over 50% of the entire length of the small intestine) required an extended enterectomy, rate of mortality in literature is specified as being 75% in such cases.

MATERIALS AND METHODS

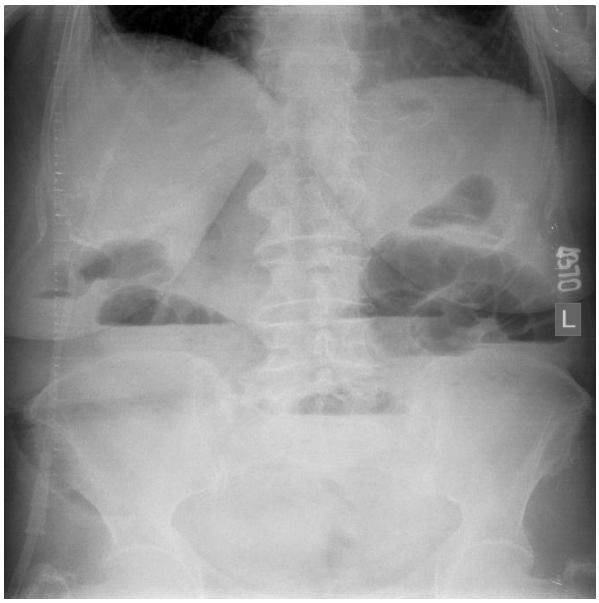
This case study is the clinical case of a patient who was admitted to the ICU postoperatively, the initial diagnose being:

- Entero-mesenteric intestinal occlusion
- Extended entero-mesenteric infarction
- Respiratory failure mechanical prosthesis
- Chronic atrial fibrillation
- NYHA Class gr .3 / 4
- Acute dehydration syndrome
- Moderate form of metabolic acidosis
- Moderate hypernatremia
- Renal functional failure

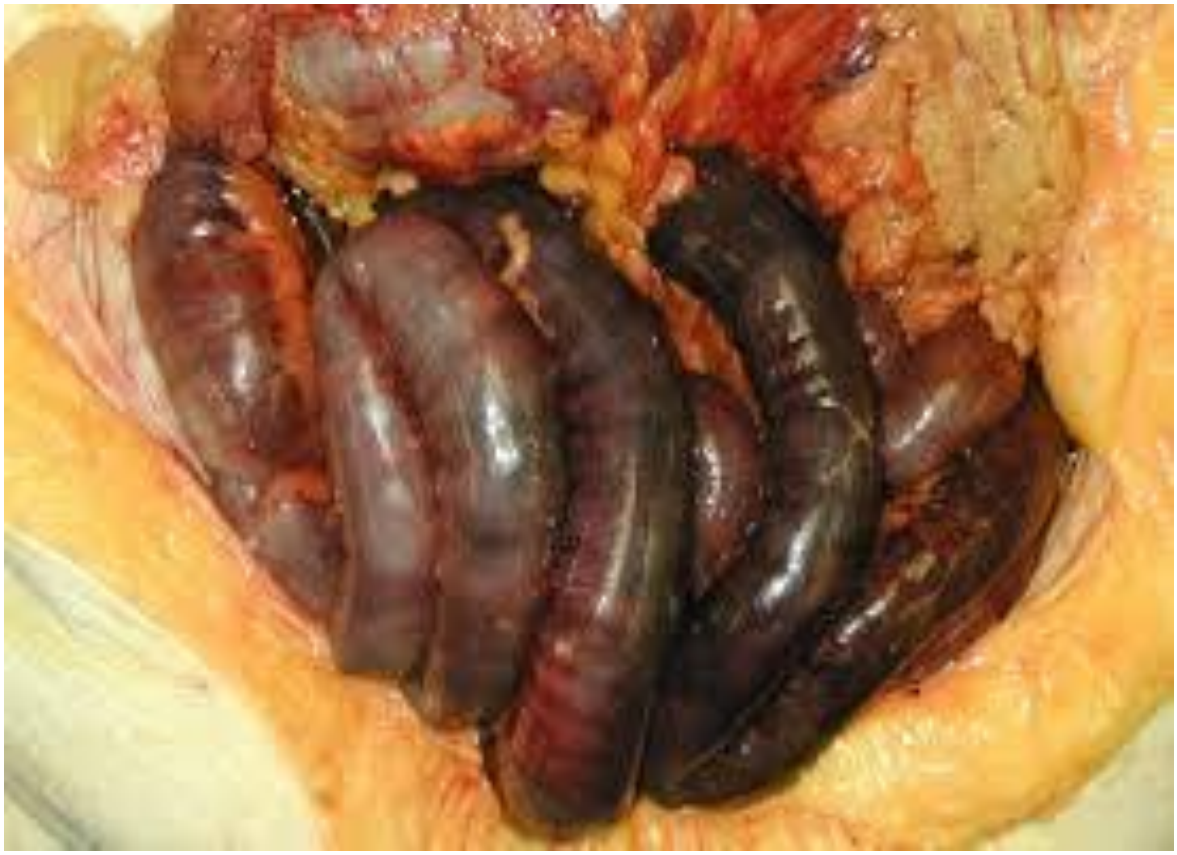
The peculiarity of this case is that the evolution described resistance to heparin therapy, rare phenomenon in clinical practice, only 1% of cases are reported when administrating heparin, the causes of failure in heparin treatment can be multiple, often is taken into account the decreased levels of antithrombin III activity.

To highlight heparin resistance, patient clinical status evolution was monitored, in particularly the relevant laboratory data.

Thus, during preoperative clinical examination, clinical cardiac decompensation signs were detected consisting of mild dyspnea, bilateral stasis rales present at the bases of both lungs, SaO2 -90% CuO 2 mask, BP 110/60 mmHg AV 120b/min, distended abdomen volume with touch sensibility. Paraclinic- examination, laboratory analysis indicates: WBC-12000, ht-45, GD-14. Fibrinogen-800mg/dl, urea 130 mg/dl, creat 1.73 mg/dl, ALT 13, AST11, Na 146mmol/l lactic acid 20mmol/l, APTT (activ prothrombin time) was 27.9 sec. empty native Rx indicates middle abdominal levels of hydro-air leakage.



Emergency intervention is undertaken, during surgery the jejunum and ileum extensive necrosis is highlighted, which is why extended enterectomy is applied, leaving in place a viable jejunum portion of about 30-35 cm and 20 cm ileum, image below was taken from the site, www.romedic.ro mirroring the real image of intestinal necrosis, exhibited during surgery.



The ICU initiates rebalancing electrolyte therapy with crystalloid solutions (0.9% sodium chloride 2000ml) and colloidal solutions (70% dextran - 500ml), then after the normalization of lactic acid, 10% glucose solutions -1000ml is added.

Antibiotics therapy is administered (started intraoperatively), consisting of the combination of antibiotics Cefort FL1 every 12h, metronidazole FL1 every 8h, gentamicin f1 every 12h, antisecretive for the prophylaxis of stress related ulcer, analgesics consisting of dexketoprofen fl1 every 12h, Perfalgan fl1 every 6h

and tramadol fl1 every 6h, and heparin therapy anticoagulants consisting of a dose of 5,000 IU (bolus) then 1,000IU/h continuous iv, APTT monitoring, control value being 27.9 sec.

Initially, the clinical evolution is favorable, the patient was extubated approximately 2 hours after surgery, effective spontaneously breathing, hemodynamically stable, diuresis resumed. 24 hours after extubation clinical condition worsens, the patient becomes hemodynamically unstable, vasopressor is administered (considering possible septic shock with abdominal starting point) Norepinephrine dose of 0.1ug/kg/min on central venous catheter fitted in the right internal jugular (Kimal triple lumen) is administered, invasive monitoring PVC and Atami (NIHON PVM-2803) are undertaken.

At this time the patient is permanently maintained on infusion therapy consisting of crystalloid and colloid solutions, adding slow intravenously digoxin f1/2 administered for heart rate control also diuretics (furosemide f2 to 12h) after restoring hemodynamics. Laboratory tests indicate in this moment 12.580 leucite and leukocytosis with 78% neutrophils, 24 TGO, TGP 12 Urea 140 mg/dL creat. 2.6mg/dl, procalcitonin 1.8 ng/ml, NA 145 mmol/lK 4 mmol/l, hg 14g/dl, ht 40%, platelets 207,000.

In terms of APTT monitoring the laboratory test used to evaluate the effectiveness of continuous heparin therapy - first checked value after 6h of treatment were 71.4 sec. proving a hypocoagulation status which is the target of therapy in case of intestinal ischemia, after that APTT values normalize despite the increase in the dose of continuously administered heparin as well as repeated 2500IU iv bolus (see table below).

At heparin levels greater than 35,000IU/day, given that the plasma activity of antithrombin III can determined (considering normal values are between 80-120%), and this plasma activity is below 60%, the phenomenon of resistance to heparin therapy can taking in consideration.

The treatment was, in this case, concentrated antithrombotic, treatment which is not yet in therapeutic use in hospitals in Romania, or fresh frozen plasma (PPP) containing a small amount of antithrombin III, given that we maintained administing heparin in large doses continuously. FFP was used in this case for patient treatment, 2 bottles every 8h (400ml/8h), 6 bottles of FFP were needed to get a response to the systemic heparin treatment, a surge in APTT's levels was observed from 46.2 sec to 126 sec, kept subsequently to between 70-80 sec throughout the heparin treatment.

RESULTS

Regarding coagulation tests, activ prothrombin time is the only time control that can be used in evaluating the effectiveness of heparin therapys' - hypocoagulation status induced by this substance, (we don't have possibilities to determine the time of anticoagulation-ACT) it's variation thereof is present in the table below.

HOUR	24	06	12	18	24	06	12
APTT (secunds)	71,2	37,6	33,3	39,5	29,6	40	41,9
HEPARIN 200 IU/ml	5ml/h	5ml/h	5ml/h	5ml/h+2500IU bolus	6ml/h+2500 IU bolus	6,5ml/h	6,5 ml/h + 2500IU bolus

HOUR	18	24	06	12	18	24	06
APTT (secunds)	47,8	49	41	40	46,2	126	92
HEPARIN 200 IU/ml	6,5ml/h	7 ml/h + FFP 2U	7,5 ml/h	7,5 ml/h + FFP 2U	7,5 ml/h + FFP 2U	7,5 ml/h	5 ml/h

Regarding patient evolution, after obtaining an adequate response to heparin therapy, it has been slowly favorable, clinical condition is gradually improving, vasopressor support is gradually decreased, lactic acid mentained at constant values up to 2 mmol/l enables the initiation of parenteral nutrition glucose 10% approx. 2g/kg/day, amino acids (10% Aminoplasmal FL1/day) 1g/kg/day and 0.5 lipid/kg/day- (Smof-lipid fl 1/day).

Plasma levels of albumin indicate, third day post surgery, severe Hypoalbuminemia, values being 2.7g/dl and its correction is required with an additional 20% hypertonic solution, dose of 1g/kg/day according to the adopted protocol. 48 hours after starting treatment with hypertonic solution of albumin 20%, plasmatic levels normalizes at 3.5 g/dl, administration being no longer necessary. During this time the patients intestinal transit resumes showing good digestive tolerance initially to liquids, which allows cardiac medication resumption after the specialist advice, followed by solid foods hence a gradual decrease of protein parenteral caloric intake. Echocardiographic examination, shows a heart with normal sized cavities with EF 40-45% with mild mitral regurgitation with a degree of pulmonary hypertension and pericardial reaction.

Patient evolution, 4th day post surgery, from the time they responded to treatment with heparin until day 11 post surgery is favorable, clinical condition good corroborated with laboratory tests showing normal levels, except INR which is prolonged due to the introduction of Sintrom (coumarin prepared administered in doses

adjusted according to the INR) after ten days of heparin therapy, transfer to the department of surgery in good clinical condition is allowed.

CONCLUSION

Resistance to treatment with heparin, a phenomenon rarely reported, some studies considered it to have an incidence rate of up to 1% in clinical practice is mainly due to decreased activity levels of antithrombin III, this rather qualitative than quantitative deficit can be determined through laboratory methods such as the chromogenic method based on the inhibition of factor 2 (thrombin).Normal values are given in percentages of 80-120%, but in practice it is virtually impossible to test, a necessary minimum 2 days ceasing of the heparin therapy is required to get good accurate results. In these conditions a favorable solution would be the introduction of another type of substance with anticoagulant role (action mechanism different from that of heparin) until antithrombin III activity is determined.

Antithrombotic decreased activity is due either to a congenital deficiency, a phenomenon rarely seen in clinical practice, antithrombin III is a glycoprotein whose synthesis is encoded by a gene located on the first chromosome, as well as in other pathological situations like systemic inflammatory syndromes (SIRS), in this case septic.

In some clinical situations, due to high doses of heparin, a decrease in antithrombin III levels may occure, it is necessary to stop the administration until the plasma concentration of antithrombin III is restored.

It should be borne in mind that in this case, elevated fibrinogen levels (considered an acute phase positive protein) showen first day after surgery and which were maintained for 6 days, led to a possible inhibitory heparin activity, the literature also indicates other acute phase proteins with similar action such as: platelet factor IV, factor VIII, histidine-rich glycoprotein.

To correct the activity levels of antithrombin III, a antithrombin concentrated solution was introduced, administered after a standardized protocol, 3000IU in bolus, slow iv, following 1500IU every 12h for 5 days, but that requires an accurate estimate of the plasma activity of antithrombin III, which means ceasing heparinoterapiei at least for 2 days.

Regarding treatment with fresh frozen plasma, the antithrombin content in this preparation form is low, maximum 70% of the value of approximately 0.12mg/dl, the required amount of FFP for antithrombin III qualitative plasma correction is considerable (this case requiring 6 bags administered in 48h), hence a less effective treatment, associated with procoagulant side-effects when compared to concentrated antithrombin III solution.

It is worth noting the role provided by the hypertonic albumin 20% solution required for the correction of severe hypoalbuminemia, given its function which has been demonstrated by numerous clinical studies regarding its important effects on colloid osmotic plasma pressure and also possibly other functions such as the transport of various substances, anti-inflammatory or antioxidant, with clinical implications in shortening the postoperative ileus and in avoiding the appearance of intestinal fistula.

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